This reminiscing review article is an account of the author’s fascination and involvements with mass spectrometry from the perspective of an organic chemist with an interest in natural product chemistry. It covers a period from 1961 through the mid 1990s as mass spectrometry evolved from a novelty technique to become a most widely used analytical technique. Following a brief synopsis of my pathway to mass spectrometry, my research efforts in this field are presented with a focus mainly on evolving principles and technologies which I had personal involvements with. To provide historical perspectives, discussions of these developments are accompanied by brief outlines of the relevant state-of-the-art, shedding light on the technical and conceptual challenges encountered during those early days in mass spectrometry. Examples are presented of my involvements with basic and applied research in mass spectrometry during graduate studies at Stanford University and close to three decade tenure in pharmaceutical research at Syntex Research. My basic research interests focused mainly on principles of electron ionization induced fragmentation mechanisms, with an emphasis on steroids and other model compounds. Extensive deuterium labeling evidence was used to determine the fragmentation mechanisms of the diagnostically significant ions in the spectra of numerous model compounds, uncovering examples of wide-ranging hydrogen transfers, skeletal rearrangements, methyl and phenyl migrations, stereoselective fragmentations and low and high energy fragmentation processes. Depiction of the industrial research phase of my career includes comments on the pivotal role mass spectrometry played on advancing modern pharmaceutical research. Examples are presented of involvements with instrumental developments and a few select cases of applied research, including studies of bile mechanisms in vertebrates, identification of bisphenol-A leaching from sterilized polycarbonate containers, high sensitivity TCDD analyses and other projects. Reflecting on my services for the mass spectrometry society, involvements with the co-founding and 12 year chairing of the Asilomar Conference on Mass Spectrometry and founding of the Bay Area Mass Spectrometry regional MS discussion group, as part of my services for the mass spectrometry community, are presented in some detail.

Keywords: steroids; stable isotope labeling; fragmentation mechanisms; stereoselective fragmentation; bile steroids; TCDD; bisphenol-A; instrumental developments; Asilomar Conference on Mass Spectrometry; Bay Area Mass Spectrometry

I. INTRODUCTION

By professional training I am an organic chemist with a long standing fascination with natural product chemistry, probing the chemical bounties and mysteries of Mother Nature. Synthetic organic chemistry and natural product chemistry share a fundamental need for structural elucidations. In the late 1950s and at the beginning of the 1960s there were only a limited number of readily available analytical tools for structure identifications. These included IR and UV spectroscopy, combustion-based elemental analyses and for configurational studies optical rotation, optical rotatory dispersion (ORD) and circular dichroism (CD). NMR spectroscopy was in baby shoes with the introduction of the first commercial 60 MHz instruments by Varian, Palo Alto, CA in 1961. The low sensitivity of these NMR instruments, requiring 20 mg or more samples for a meaningful analysis, prevented their application to samples available only from small scale preparations. NMR gained widespread use later in the 1960s with the introduction of the 100 MHz and Fourier Transform (FT) instruments which reduced the sample requirement by ten fold and provided far more structural information.

In search for new analytical methods, attention turned to mass spectrometry (MS) as a technique with potentials to provide a wealth of structural information on sub-milligram amount of samples. Mass spectrometry had been in use already during and after the Second World War in the petroleum industry to analyze volatile hydrocarbons. In the 1950s a select group of pioneering investigators experimented with its application to non-petrochemical, lower volatility compounds demonstrating its potential usefulness in general organic chemistry. Their reports were impressive and by the time I started my graduate studies in 1961 mass spectrometry was already considered an exciting new technique with great potentials for becoming a major analytical tool for structural elucidations. In this review I intend to show how I succumbed to this appeal and how mass spectrometry became my career long scientific interest.

My involvement in this field spans the period from mass spectrometry being the domain of mostly spectroscopists, physicists and geochemists, through its evolution to become a most widely used analytical technique with current applications in virtually every scientific and medical field. This review focuses on developments in organic chemistry applications which I had personal involvements with, including comments on their relevance to the contemporary state-of-the-art. A brief
overview of some of my research contributions in this field is presented, concentrating more on conceptual descriptions rather than technical details, followed by examples of applications of mass spectrometry in the pharmaceutical industry and the role this technique played in the advancement of modern pharmaceutical research.

During the second half of the 20th century, exponential growth in the use and instrumental developments in mass spectrometry created a rapidly growing scientific community dedicated to this field. My contributions to the professionalism of this emerging society are outlined in Section V. Two contributions with lasting consequence for the society, the co-founding and 12 year chairing of the Asilomar Conference on Mass Spectrometry, an international research conference series, and involvements with the founding of Bay Area Mass Spectrometry, a regional MS discussion group, are discussed in some detail in Sections V(A) and V(B).

II. PATHWAY TO MASS SPECTROMETRY

Sharing an incident commonly mentioned in the autobiographies of many noted scientists who were born in the first half of the 20th century, and so eloquently depicted by Oliver Sacks in his epic biographical book, “Uncle Tungsten; Memories of a Chemical Boyhood” (Sacks, 2001), I too got interested in chemistry by having received a chemistry kit at age 11. In 1948, in the war ravaged city of Budapest, Hungary, this kit was prepared by an entrepreneurial young man who had a complete disregard, or lack of comprehension, of safety considerations. It came with no instructions other then brief identification of the chemicals and most of my experiments were based on trial-and-error, or by following often boisterous suggestions of other kids who learned the means of creating visual, audio or olfactory effects. This was an opportunity for exciting experimentations with “chemistry in the raw” and, of course, led to frequent disapprovals by our household members. However, these early experimentations and the sharing of excitement with likeminded peers had a major impact on the development of my scientific curiosity.

In 1951, my school education in Budapest was interrupted at the end of grade 8 by political upheavals in the communist regime during its darkest Stalinist period in Hungary. Our family was deported to a small town where I had to resort to heavy physical labor for our survival. The political repression eased in 1953 and we were allowed to return to the outskirts of Budapest. In 1954, at age 17, I got my first career related job as a laboratory assistant at Chinoin Pharmaceutical and Chemical Company in Budapest, which was one of the largest pharmaceutical companies in Hungary. It was only with the help of a distant relative who worked at Chinoin that I managed to get this job since I lacked any credential to show alignment with the prevailing political ideology of communist youth movements which at that time was a prerequisite for getting into any position other than menial jobs. At Chinoin I got an accelerated training in the fundamentals of analytical and synthetic chemistry and after work I attended evening sessions at the Technical School of Chemistry, a specialized high school for working adults. The laboratory I worked in at Chinoin provided support for the division which amongst other functions was involved with the isolation of natural products from various sources, heparin from bovine blood, estrogens from pregnant mare urine, etc. This work was a tremendously informative and exciting experience for me and led to my career decision to become a chemist. A dramatic change in this phase of my life occurred on October 23, 1956. As I was preparing a laboratory scale batch of 17α-ethynyl-estradiol the news broke that thousands of people were gathering in front of the Parliament building, demanding freedom of the press and other issues which were delineated in a ten point declaration. I left work in a hurry and headed to the Parliament where I witnessed what had become the start of the 1956 Hungarian Revolution against the Soviet occupation. That was the last day I set foot in Chinoin as an employee.

After a brief period of gaining freedom, on November 4 the revolution was brutally crushed by the invading Soviet Army. Due to concerns for my safety in Budapest and the obvious return of political repression in the country, on December 26 I decided to join the exodus of some two hundred thousand refugees from Hungary with the then living members of my family—mother, younger brother and an older cousin. After an all night march in pitch dark, through deep-plowed fields covered with two feet of snow, and dodging the occasional search lights and wildly shooting inebriated Russian border patrols by hiding in the snow, we were fortunate to make it to Austria on our first trial—bloodied by frost bites but free at last. We stayed in Austria for 6 months in refugee camps but by this time the US quota for Hungarian immigrants was already full. However, with the aid of an affidavit from a distant relative living in California, and most probably by the insistence of my brother and I that we wanted to attend university in the USA, in June 1957 we were allowed to immigrate to the US as a “family consolidation” case. My brother, Zoltán A. Tökés, in time became a Professor of Biochemistry & Molecular Biology at the Keck School of Medicine, University of Southern California in Los Angeles. With his and my modest contributions to science we did our best to compensate our adopted home country for the opportunities provided to us.

Within days after our arrival in California I landed a janitorial job at the Queen of Angels Hospital in Los Angeles and attended English classes for foreigners in the evenings. A fortuitous event while attending these English classes led to a pivotal change in my career development. My teacher, after learning about my interest in chemistry, introduced me to her husband’s friend, Professor Norman Kharasch of the Department of Chemistry, University of Southern California (USC). After my interview with Professor Kharasch he immediately offered me a job as a lab assistant and helped me to get a full tuition scholarship for my undergraduate studies at USC. With the exception of summer recesses, I continued working in his laboratory during the four years of my undergraduate studies at USC.

My undergraduate work at USC was very busy with full loads of course work, part time work in the laboratory, all while learning English. I took most of the science and math classes in my first and second years and I struggled with English literature, history and philosophy classes during my third and fourth years. But most importantly, I was back in doing synthetic and natural product chemistry, synthesizing thyroxin and its various sulfur analogs and other natural products (Kharasch et al., 1962). During the summer recesses of 1958 and 1959, I had a stint again with industrial chemistry by working as a chemist at CycloChemical Corporation in Los Angeles’. During the summers of 1960 and 1961 I worked in the laboratory of Professor Paul Saunders in the Pharmacology Department of USC where I built a gel electrophoresis apparatus and carried
out isolation and characterization of the lethal fraction in the venom of stonefish, *Cynanceja horrida* (Saunders & Tókés, 1961). This work was of considerable interest to the US Navy and Marines because this fish presented a potential hazard to their personnel. By the time I graduated in 1961 with a BA degree in chemistry, I had two papers submitted for publication and received an American Institute of Chemists award for scholastic achievement as the highest grade point chemistry graduate of the year.

I am indebted to Milan Punić (entrepreneur, business tycoon, founder, President, CEO and Chairman of ICN Pharmaceuticals, Prime Minister of the Federal Republic of Yugoslavia in 1992–3), who in 1958 as a young Yugoslavian émigré chemist was a colleague at CycloChemical Co. and provided me ride to and from work in his 2-seater subcompact Nash Metropolitan car.

My undergraduate records helped me to get a full tuition scholarship for graduate studies in the Department of Chemistry of Stanford University where I earned my living with the aid of teaching and research assistantship grants. During the end of the 1950s, the chemistry department at Stanford had undergone a significant expansion and with the addition of several distinguished staff members the department provided a truly stimulating research environment in a variety of fields. There was a strong emphasis on synthetic and natural product chemistry and I became interested in the work of Professor Carl Djerassi whose research interests spanned synthetic and natural product chemistry as well as the development and applications of newer analytical techniques, including optical rotary dispersion (ORD), circular dichroism (CD), magnetic circular dichroism (MCD) and mass spectrometry. I was most intrigued by his research in mass spectrometry since it appeared to have great potentials for becoming a major new analytical tool for structural elucidation of organic compounds.

**III. BASIC RESEARCH IN MASS SPECTROMETRY**

Prior to 1960 organic chemistry related research in mass spectrometry was carried out primarily in a few select universities and research institutes. The scope of these applications was generally limited to compounds which could be readily volatilized by heating under vacuum. The unique power of this technique to provide exact molecular weights, and with high resolution measurements elemental compositions, had been well recognized and investigative studies to correlate fragmentation patterns with structural features were carried out using simple model compounds. However, there were hardly any reports on the utilization of the diagnostically important fragmentation patterns in the structure elucidation of unknown compounds. Searching for means to allow reliable exploitation of these diagnostic spectral features, I became interested in studying the mechanism of these fragmentations in classes of compounds which have frequent needs for structure identification of unknown samples.

During this period there were two types of commercial mass spectrometers in use, the time-of-flight and magnetic sector based instruments. The most commonly used instruments for organic chemical applications were the magnetic sector instruments with electron-impact ionization mode (EI) at 70 eV ionization potential. In certain cases lower ionization potentials were used to enhance the intensity of molecular ions of fragmentation-prone compounds, although usually at the sacrifice of sensitivity. In the 1950s some basic concepts of fragmentation mechanisms had been reported already by the pioneering works of research groups led by J.H. Beynon and R.I. Reed in the UK, J.D. Morrison in Australia, R. Ryhage and E. Stenhagen in Sweden, V. Tal'rose in the USSR, V. Hanus in Czechoslovakia, E.C. Homing, H. Fales, F. Fields, B. Munson, F.W. McLafferty, K. Biemann and A.G. Sharkey in the US to name a few. It was recognized that the fragmentation of ionized molecules generated by electron ionization follow energetically rational pathways, and the concept of charge localization on the part of the molecules with the lowest ionization potential as a primary fragmentation triggering step had gained widespread acceptance. With these advances basic fragmentations of some simple molecules could be already predicted, a prime example being the well established McLafferty rearrangement of aliphatic ketones (McLafferty, 1959). Theoretical considerations of fragmentation mechanisms have been proposed as early as 1952 (Quasi-equilibrium theory of Rosenstock et al., 1952), followed by several revisions, but these could be applied only to well studied model compounds and provided no help for the structure elucidation of unknown samples. Various speculative concepts floated, like “hydrogen soup” and “structural scrambling” which implied structural randomization before or during fragmentations, weren’t helpful either. Consequently, there was an urgent need for more detailed studies of the factors affecting the fragmentation of ionized molecules having single or multiple functional groups, rigid or flexible skeletons, and for an examination of the general fragmentation characteristics of various classes of natural products.

Spurred by previously reported successes and access to improved instruments, the beginning of the 1960s opened the floodgate to reports on the application of mass spectrometry in a variety of fields in both synthetic and natural product chemistry. The number of research publications skyrocketed and some of the most influential books promoting organic chemical applications became available (Beynon, 1960; Biemann, 1962; McLafferty, 1963, and 3 volumes by Budzickiewicz, Djerassi, & Williams, 1964a,b). At my arrival at Stanford in 1961 Professor Djerassi’s research group was a hotbed of activities for investigating the subtleties of EI induced fragmentation mechanisms. There were a number of graduate students and post doctoral fellows from all over the world working on these projects and many of them later became leading primary investigators in this field. I was caught up with the excitement of these activities and joined Carl Djerassi for my PhD dissertation research in mass spectrometry. In addition to pursuing the primary goal of uncovering basic principles beneficial for practical applications, I was also fascinated by the power of mass spectrometry to provide an intimate view of the behavior of isolated, electronically excited molecules in the gas phase, acting in a completely reproducible manner for a given energy and time frame. In the ensuing discussions I do not intend to list all my accomplishments in basic research, I just present some illustrative examples of significant observations as they relate to basic concepts of interest at the time.

The focus of the Djerassi group’s program at the beginning of the 1960s was a systematic study of the fragmentation directing effects of various functional groups on the steroid skeleton and other model compounds. I embarked on studying the fragmentation mechanisms of mono functional steroidal ketone model compounds. In practice this meant that I had to synthesize the model compounds and a large number of site-specific deuterium labeled analogs to establish the cleavage sites and to shed light on the fragmentation mechanisms which...
usually involve one or more hydrogen transfers. Consequently, I had to develop a considerable expertise in deuterium labeling techniques and the associated synthetic work was reported mostly as parts of our mass spectrometry publications (Tökés & Throop, 1972; Throop & Tökés, 1967; Cowen et al., 1976).

The model compounds I started with were 5α-pregnan-12-one (1) and 5α-pregnan-20-one (5). In addition to the intrinsic interest in their fragmentation characteristics, these model compounds were also of interest as they may provide information about the interatomic distance requirements between the γ-hydrogen and the oxygen atom in McLafferty rearrangements. These ketones have γ-hydrogens at the C20 and C12 positions, respectively, in fixed distances to the oxygen atom, and both compounds exhibit prominent ring D cleavage products which a priori could be initiated by a McLafferty rearrangement (see ions of m/z 233 and 217 in Figs. 1 and 2, respectively). Previous studies indicated that McLafferty rearrangements proceed if the interatomic distance between the oxygen and γ-hydrogen is 1.5 Å, or less than 1.8 Å. The O – H interatomic distance in these ketones, as estimated from Dreiding models, being around 3 Å, it was considered forbiddingly high and McLafferty rearrangement was not expected to participate in the formation of the prominent ring D cleavage products. It was surprising, therefore, that in pregnan-12-one 90% of the hydrogen transferred to the charge retaining fragment was found to originate from the C20 position. This indicates that instead of an initial McLafferty rearrangement (Scheme 1, sequence a) the loss of ring D in this compound involves an initial homolytic fission of the strained 13–17 bond (2, sequence b), thereby allowing close proximity of the C12 oxygen to the C20 hydrogens which are activated by the adjacent C17 radical site. Transfer of one of the C20 hydrogens leads to a conjugated oxonium ion (3) which upon cleavage of the 14–15 bond yields the prominent m/z 233 fragment ion (4) (Djerassi & Tökés, 1966).

In 5α-pregnan-20-one (5) the prominent ring D cleavage proceeds by a multitude of mechanisms yielding fragments ions with charge retention on either the tricyclic hydrocarbon or the oxygen bearing fragments (see cleavage patterns indicated on structure 5). As expected, deuterium labeling revealed no major loss of label from C12 or C18, the two positions with γ-hydrogens to the C20 oxygen, in the formation of the hydrocarbon fragment, eliminating McLafferty rearrangement as the triggering step for the loss of ring D and an extra hydrogen. The source of this hydrogen is varied but 40% of it was found to originate from the 8β-position. The formation of the oxygen bearing fragment (m/z 84 in Fig. 2) involves reciprocal hydrogen transfers with hydrogens at C12, C18 and other sites being contributors from the hydrocarbon side and C16 being the main source for the reverse transfer step. These observations are again indicative of an initial rupture of the strained 13–17 bond in

**FIGURE 1.** Mass spectrum of 5α-pregnan-12-one (EI, 70 eV).

**FIGURE 2.** Mass spectrum of 5α-pregnan-20-one (EI, 70 eV).
17β-side chain bearing steroids (Scheme 2). This hypothesis is supported by the observed lower intensity of these ring D fragmentation products in the 17α-epimer of 8 in which the 13–17 bond is sterically less strained. After fission of the 13–17 bond (6) the resulting C17 radical can swing around to pick up a hydrogen from various sites and in case of the 8β-position this process yields a conjugated tertiary carbonium ion of m/z 217 (7) (Tökés, LaLonde & Djerassi, 1967b).

As part of these studies of the 12- and 20-keto-pregnane model compounds, we presented mechanistic proposals for the genesis of all diagnostically significant ions in their spectra. In an analogous manner, we then extended our studies to mono-functional androstane derivatives, 5α-androstan-12-one (8) (Djerassi & Tökés, 1966) and 5α- and 5β-androstan-17-one (9) (Tökés, LaLonde & Djerassi, 1967a), and then to some α,β-unsaturated ketone bifunctional model compounds, 5α-pregn-9(11)-en-12-one (11), 5α-androst-9(11)-en-12-one (12) and 5α-pregn-16-en-20-one (13) (Tökés & Djerassi, 1965). Again, with the aid of deuterium labeling evidence we examined all diagnostically significant ions in their spectra and proposed fragmentation mechanisms wherever it was possible.

During all these studies it became increasingly evident that a detailed study of the fundamental fragmentation behavior of the steroid skeleton was needed, with an emphasis on the prominent and diagnostically important ring D cleavage of C17 side chain bearing steroids (ions m/z 217 and 218 in Figs. 3 and 4). Earlier reports on steroid skeletal fragmentations were based mostly on speculative rationalizations which our studies proved to be incorrect or only partially correct. We have undertaken a detailed study of side chain bearing steroidal hydrocarbons, represented by C5-epimeric pregnanes (14 and 15) and 5α-cholestan (16) model compounds, utilizing extensive deuterium labeling support in both series (Tökés, Jones & Djerassi, 1968).
Primary fission of the highly strained 13–17 bond (18) in these compounds triggers the formation of the majority of the diagnostically significant fragment ions, including the prominent ring D cleavage products of m/z 217 and 218 (see Figs. 3 and 4). During this bond fission the charge remains on the C13 tertiary carbon and the side-chain-bearing C17 radical can then swing around to pick up a hydrogen from various sites. Our deuterium labeling results ascertained that the genesis of the dominant m/z 217 fragment ion involves several different mechanisms since the expelled extra hydrogen originates from various sites. The major transfer site (49–59%) is the a priori unexpected 14α-position (Scheme 3, process a), yielding an ionized olefin intermediate (19) which then undergoes further rearrangements to facilitate the ultimate cleavage of the 14–15 bond. One possibility may involve a hydrogen migration from the 8β-position to C-14, leading to the formation of conjugated fragment ion 20. Other observed hydrogen transfer sites include the 7, 8β, 9α, 12 and 18 positions and we proposed mechanistic possibilities for all these fragmentation processes.

Our deuterium labeling results revealed also that the genesis of the accompanying m/z 218 fragment ion, which formally doesn’t require the involvement of any hydrogen transfer, in fact proceeds via a highly site-specific reciprocal hydrogen transfer process. The majority of this ion (82%) is formed by the transfer of a hydrogen from the C18 angular methyl group to the C17 radical site in intermediate 18 (Scheme 3, process b), followed by a reverse hydrogen transfer from C16 (21) to facilitate cleavage of the 14–15 bond, yielding an ionized (22) and a neutral olefin fragment. Intermediate 21 is also involved in the genesis of a minor portion (6%) of the m/z 217 ion by direct cleavage of the 14–15 bond.

Next, we undertook detailed examination of the fragmentation behavior of the basic steroid skeleton, 5α-androstan-3β-ol (10) (Tokés & Djerassi, 1969). This study exposed the vast complexity of these hydrocarbon fragmentations due to the lack of any dominant charge localizing site on these molecules. As expected, this tetracyclic system, which lacks even an exceptionally strained bond like the cleavage prone 13–17 bond in 17β-side chain bearing steroids, shows fragmentations in various parts of the molecule in comparable intensities. The only way this molecule can lose a fragment by a single bond-cleavage is the expulsion of one of the two angular methyl groups. These methyl losses were found to be the sole contributors to the [M - CH3]+ ion, in a 3:2 preference for the loss of C18. It is possible
that these single bond cleavage products undergo further skeletal rearrangements to stabilize the resulting fragment ions. Having labeled with deuterium 14 of the 17 hydrogen-bearing positions in this molecule allowed assignments of the cleavage sites for most fragment ions in the diagnostic region of the spectrum. It also revealed that the genesis of most of these ions involve multiple cleavage processes and extensive hydrogen transfer steps. Only with such extensive deuterium labeling evidence was it possible to detect the participation of reciprocal hydrogen transfers in cleavages which formally involve only the fission of two bonds in losing a part of the molecule. An example of such a cleavage is the reciprocal hydrogen transfers from the C19 and C3 positions in the loss of ring A to yield fragment ion m/z 204 (25). The most likely mechanism for this process is depicted in Scheme 4. The primary radical formed by fission of the 1–10 bond (23a) is relieved by hydrogen transfer from the C19 angular methyl group which is activated by the adjacent positive charge at C10. Loss of ring A is then facilitated by the back transfer of a hydrogen in a 6-member transition from C3 (24) to yield an ionized (25) and a neutral (26) olefinic fragment.

An alternative process for the loss of ring A, which yields fragment ion of m/z 203, involves the loss of an extra hydrogen and is an example of the complexity of these hydrocarbon fragmentations. The major source (70%) of this extra hydrogen is the activated 5α-position (23b), which is also the site of a subsequent C-C bond cleavage. This implies that other hydrogen migrations or skeletal rearrangements are involved in the charge retaining part of the molecule to facilitate the formation of charge-stabilized fragment ions. One possible mechanism is depicted in Scheme 5 involving a 1–2 shift of one of the C6 hydrogens to C5 (27) which upon expulsion of the ring A moiety (28) leads to the formation of an allylically stabilized tertiary carbonium ion (29). This observation is analogous to the loss of the 14α–hydrogen (19) in the genesis of the m/z 217 ion in 17β-side chain bearing hydrocarbons (see path a in Scheme 3), a process which also involves the subsequent cleavage of the 14–15 bond in the loss of ring D. We proposed mechanistic interpretations for the genesis of most diagnostic fragment ions in the spectrum of 5α-androstan (Tókés & Djerassi, 1969).

During these studies we observed instrument related variations in the spectral features of these hydrocarbons. For example, the 70 eV EI spectrum of 5α-pregnane varied considerably when measured on three different instruments, Atlas CH-4, CEC 21-103C and AEI MS-9 (Tókés, Jones & Djerassi, 1968).
Such instrument dependent spectral variations have been reported earlier and with cholestane by Spiteller-Friedmann, Eggers & Spiteller, 1964. This is caused by variations in thermal and/or metal catalyzed decomposition of hydrocarbons resulting from differences in the ion source or sample insertion designs of these instruments.

At Syntax I continued my involvement with basic research in mass spectrometry, although to a limited extent. Pursuing my interest in steroid skeletal fragmentations we investigated a stereospecific fragmentation which is diagnostic for the configuration of the A/B ring junction of C17 side chain bearing hydrocarbons (Tokés & Amos, 1972). The m/z 149–152 region in the mass spectra of these compounds exhibit one or two intense peaks at m/z 149 and 151 depending on the configuration at C5 (compare Figs. 3 and 4). The ubiquitous m/z 149 ion is present in the spectra of both 5α- and 5β-hydrocarbons and is due to several complex fragmentation processes. Even with the extensive deuterium labeling evidence we reported earlier (Tokés, Jones & Djerassi, 1968) it was still impossible to identify the exact cleavage patterns responsible for this ion, and 13C labeling of key tertiary positions will be needed to shed further light on their genesis. This is in part due to the fact that retention or loss of a deuterium in a tertiary position cannot be used to ascertain the presence or absence of the associated carbon atom in the charge retaining fragment.

The diagnostically significant m/z 151 ion, which is prevailing only in the spectra of C17 side chain bearing 5β-steroids, is a stereospecific cleavage product indicative of cis configuration at the AB ring junction. Again, the genesis of this ion involves multiple cleavage processes but the majority of it is due to the loss of rings C and D by fissions of the 8–14 and 9–11 bonds and the transfer of a hydrogen to the charge retaining fragment. In accordance with the well established ring D fragmentation described above, the need for a C17 substituent for this fragmentation to occur is indicative of the participation of 13–17 bond fission (30). A possible mechanism for the genesis of a major portion of this ion is depicted in Scheme 6 (Tokés & Amos, 1972). Rupture of the activated 8–14 bond in intermediate 30 yields intermediate 31 in which transfer of a hydrogen from the resulting open-chain part of the former rings C and D portion of the molecule leads to the concomitant cleavage of the 9–11 bond. About 50% of this hydrogen transfer was found to originate from the allylic C12 position yielding fragment ion 32 and an expelled diene radical 33. Both of these fragments are expected to undergo further rearrangements or fragmentations to stabilize their positive charge and radical sites, respectively. Possible examples are tertiary (32a) and homoallylically stabilized (32b) carbonium ions. Inspection of Dreiding models of ion 31 and its 5α-epimer, revealed that the stereospecificity of this cleavage is apparently due to facile access by the C17 radical to the 5α tertiary hydrogen, but approach to the 5β-hydrogen is prevented by overlaps with various parts of the molecule, leading thereby to the pathway shown in Scheme 6. In fact, transfer of the 5α-hydrogen was found to be the major contributor to the formation of the m/z 149 ion, as confirmed by the 70% loss of deuterium from this position in 5α-cholestan (Tokés, Jones & Djerassi, 1968).

Next, we have undertaken a detailed study of the EI induced fragmentation of C5-unsaturated steroids, including cholesterol (Wyllie, Amos & Tokés, 1977). Cholesterol has been one of the most commonly used samples in mass spectrometry yet study of its fragmentation behavior and associated mechanisms have been mostly ignored or discussed based only on speculations. Our study with the use of extensive isotope labeling evidence revealed that the characteristic fragmentations in these molecules are triggered primarily by the C5-double bond, and that previous speculative interpretations were mostly wrong. The presence of this double bond initiates very extensive skeletal rearrangements in the rings A and B portion of the molecule, akin to what can be expected in photochemical type rearrangements. A most striking example of the complexity of these fragmentations is the genesis of the significant fragment ion at m/z 301 in the spectra of both cholesterol (33) and cholest-5-ene (34). Several different cleavage patterns have been proposed previously for the formation of this ion, without labeling evidence or mechanistic considerations. With the aid of 13 deuterium labeled and structural analogs of cholesterol we determined that none of these speculative proposals are correct and this fragmentation proceeds via a ring A and B cleavage pattern which is a priory a most unexpected process as depicted on structure 33. It entails the loss of ring A together with C5 and an extra hydrogen. Formally, this requires cleavages of both the double and a single C-C bond of C5 and quite unexpectedly the major source of the extra hydrogen is the adjacent C6 vinlylic position.

![SCHEME 6.](Image)
Possible mechanisms for the genesis of this ion, involving a major (55%) and a minor (7%) source of the hydrogen loss from the C6 and 9α positions are shown in Scheme 7, paths a and b, leading to allylicly stabilized ions 40 and 42, respectively. Initial reports on these findings have been presented in 1970 at the Pacific Conference on Chemistry and Spectroscopy in San Francisco, CA and at the Royal Australian Chemical Institute Conference in Canberra, Australia. These findings have been confirmed by a subsequent analysis of a commercial sample of 4-13C-cholesterol and by an independent study of the analogous fragmentation behavior of androst-5-en-3β-ol (Budzikiewicz & Ockels, 1976). For the androstene study the authors provided extensive deuterium labeling evidence but no mechanistic proposals. My last involvement with mechanistic studies in the steroid series was a collaboration in a tri-Continental joint investigation of translational energy releases associated with the loss of the C18 vs. C19 angular methyl groups in cholesterol and related steroids. This study established that the translational energy release is higher with the loss of the C18 radical from both M⁺ and [M – H2O]⁺ ions (Zaretskii et al., 1986).

Other EI induced fragmentation studies I have been involved with at Stanford and Syntex, which yielded conceptually important revelations, include a variety of non-steroidal model compounds. At Stanford, a study of the spectra of trans-2-furfurylidene-9-methyl-1-decalone (43) and related analogs revealed examples of EI induced methyl migrations, posing a potential limitation in the use of fragmentation patterns for the structure elucidation of unknown compounds (Djerassi et al., 1966). The base peak in the spectrum of this compound is at m/z 121 and with the aid of deuterium and substituent labeled analogs we established that this ion consists of the furfurylidene moiety together with two of the ring carbons and the angular methyl group. We proposed a mechanism for this fragmentation, shown in Scheme 8, which involves initial loss of CO from the molecular ion, followed by a 1,2 methyl shift in intermediate 44 and concomitant bond cleavages as shown on structure 45 leading to the fully conjugated m/z 121 fragment ion 46.

At Syntex, our attention turned to examples of EI induced phenyl migrations and cases of extensive long range structural rearrangements which can complicate spectral interpretations. One pertinent example we encountered was during our study of a series of 1,5-diphenyl-1,2-dihydropyrazine-2-one (47) analogs. The molecular ion is the base peak in these spectra, and the most intense fragment ion is due to the loss of CO, leading to the corresponding 1,4-diphenylimidazoles (48). This transition was confirmed by linked scan metastable peak measurements and by
comparison of the spectrum of 47 with that of an authentic sample of 48, both showing identical fragmentation patterns. A noteworthy feature in these spectra is the presence of a significant peak at m/z 165 which we identified as fluorenyl cation 51. A possible mechanism for the genesis of this ion involves a diphenyl aziridine intermediate 49, in which the phenyl group on the nitrogen shifts to the adjacent benzylic carbon to yield isomeric form 50. Extensive rearrangements and interactions between the two formally distant phenyl groups then lead to fragment ion 51 (Scheme 9). Precedents for similar interactions between adjacent phenyl groups have been reported in the literature. We proposed possible mechanisms for the formation of all other noteworthy fragment ions also in the spectra of these analogs (Ackrell et al., 1979).

Other classes of compounds we studied which exhibit phenyl migrations and interactions between isolated phenyl groups include series of phosphinyl stabilized triphenylphosphonium ylids and their isoelectronic variants N-phenylimino-triphenylphosphorane analogs as exemplified by model compounds 52 and 54, respectively. In both series these compounds exhibit intense molecular ion peaks and fragmentation products typical of the presence of a triphenylphosphoryl moiety. A common feature of these compounds is the formation of a prominent [M – H]⁺ ion, which is generated by a high-energy rearrangement process as indicated by their rapid disappearance on lowering the ionization potential. In accordance with earlier reports on the fragmentation of other triphenylphosphoryl derivatives, the most likely structures of these [M – H]⁺ ions are analogues of ion 55 in the iminophosphorane series (Tókés & Jones, 1975). This postulate is supported by the observed subsequent cleavage products which involve linked phenyl structures in both series. In the spectra of the triphenylphosphonium ylid analogues 52 the most abundant ion is a product of a facile long range phenyl migration step. These ions are formed by 1,3-migration of one of the phosphonate phenyl groups to the charge retaining fragment with concomitant expulsion of phenyl metaphosphate as shown on structure 52. This rearrangement yields highly conjugated fragment ions, as exemplified by ion 53, and involves a low-energy process since these ions remain the only prominent feature in the spectra even at low ionizing voltages (Tókés & Wong, 1970).

The wealth of information generated by these mass spectrometric fragmentation studies in the Djerassi group was shared with another Stanford team, headed by Professors Joshua Lederman and Edward Feigenbaum, in a collaborative effort to develop potential organic chemistry applications for DENDRAL, an “artificial intelligence” project (Lindsay et al., 1980). While generating various programs for the DENDRAL project, attempts were made to develop heuristic data interpretations for maximizing the information content derivable from mass spectral data, and programs like CONGEN have been generated for trials. Ultimately, the observed complexity of EI induced fragmentations, increasing popularity of alternate ionization modes, and advances in low-cost massive data storage and real time data management capabilities diminished interest in these developments and spectral comparison based data interpretation programs gained acceptance. Large commercial data files and software for facile spectrum matching searches became available from various commercial sources, and instrument manufacturers proceeded to include these as part of their data management packages. However, understanding the fragmentation mechanisms in mass spectral analyses remained important in the structural elucidation of unknown synthetic and natural products and in biopolymer sequence analyses. For many of us, early day researchers, involvement with these fundamental studies was a fascinating part of our career, pushing the frontiers of mass spectrometry.
IV. MASS SPECTROMETRY IN PHARMACEUTICAL RESEARCH

After a brief postdoctoral term as a CNRS Fellow at the University of Strasbourg in France, in 1966 I was invited to join Syntex Research in Palo Alto, California to direct the operation of their mass spectrometry laboratory. Syntex was a relatively young pharmaceutical company, founded in Mexico in 1944 with the discovery that a natural product readily available from a local yam could be converted into progesterone. This discovery opened the door for the industrial scale production of this valuable starting material for the synthesis of cortisone in 1951, and in close succession of norethindrone, the first orally active ingredient for the birth control pill. Between 1952 and 1957 Djerassi assumed intermittent faculty positions at Wayne State University in Michigan and in 1959 he moved to Stanford University as Professor in the Department of Chemistry. He retained his affiliation with Syntex and in 1963 he was instrumental in bringing its research Department of Chemistry. He retained his affiliation with Syntex in 1959 he moved to Stanford University as Professor in the Department of Chemistry. He retained his affiliation with Syntex and in 1963 he was instrumental in bringing its research operations to Palo Alto. During the following years Syntex gained further recognition as it became a full fledged pharmaceutical company by bringing to market two steroidial products, the birth control pill Norinyl® and a potent corticoidal anti-inflammatory ointment Synalar®. Syntex Corporation was managed by scientists and cultivated an academic-style research environment which I found attractive for starting my research career. Having met some of Syntex’s staff during my graduate studies at Stanford, and being familiar with their impressive research accomplishments, it was an easy decision to accept their invitation.

A. Instrumentation

When I arrived at Syntex in 1966 the MS facility consisted of a venerable Atlas CH-4 mass spectrometer (Atlas MAT GmbH, Bremen, Germany) and an experienced laboratory technician, John W. Smith. John transferred from the Djerassi laboratory at Stanford where he was involved with analyzing some of my samples during my graduate research work. He proved to be a major asset for Syntex since in those days the operation and maintenance of a mass spectrometer required ability to read circuit diagrams, soldering and other electromechanical skills more than chemical knowledge. Our CH-4 came equipped with vacuum-tube based magnet power supply, and TO-4 ion source where the sample in a graphite crucible was inserted into a cartridge, called a “boat,” which constituted part of the ion source assembly. Its vacuum system included two mercury diffusion pumps with liquid nitrogen cooled condensers. Sample insertion required sequential fore- and high-vacuum pumping before the ion source chamber could be opened to the analyzer. The cartridge and ion source components required frequent cleaning which involved the complete disassembling and reassembling of these delicate parts. When everything functioned well, running a dozen or more samples a day was considered a good accomplishment.

Sample introduction, in general, was cumbersome in those days. For example, the CEC 21-103C instrument at Stanford used a batch-inlet system, involving sample evaporation from a heated and evacuated glass bulb container, and the AEI MS-9 instrument used a cumbersome glass capillary system. After my arrival at Syntex, we embarked on upgrading our instrumentation and acquired another Dempster-type sector instrument, the Varian MAT CH-7 (Bremen, Germany), which featured oil diffusion pumps and a more efficient and facile temperature-controlled direct inlet sample probe. We also implemented several upgrades to the CH-4; switched to using reusable gold and quartz crucibles, installed a transistorized magnet power supply, an EFO-4B ion source with a water-cooled direct inlet probe, replaced the mercury pumps with turbomolecular pumps, and this instrument continued providing good service for more than fourteen years. Introduction of the turbomolecular pumps was a welcomed advance, but the early models were finicky, tended to disintegrate without obvious reasons, and prompted frequent commiseration among unlucky users about the dire consequences of pulverized fans.

Next, our attention turned to interfacing a gas chromatograph (GC) with a mass spectrometer (GC/MS). Early attempts with GC/MS experimentsations started in the 1957–59 period when Roland Gohlke and Fred McLafferty diverted a small fraction of the GC effluent into a Bendix time-of-flight mass spectrometer. Reports of the first practical GC interface with a magnetic sector instrument appeared in the mid 1960s primarily by the pioneering work of Ragnar Ryhage, Royal Karolinska Institute, Stockholm and Einar Stenhagen, University of Upsala in Sweden. Their goal was to develop an instrument to aid pharmacokinetic studies which was a most daunting task those days. The Swedish team developed a stainless steel jet separator interface to eliminate the high-flowrate carrier gas associated with packed column GC technology, and then commercialized the resulting GC/MS system through the Swedish company LKB (Bromma, Sweden). Other instrument manufacturers followed suit using different interfaces and GC/MS gained immediate widespread use. Encouraged by these reports, we set out to interface our CH-7 mass spectrometer with an HP F&M-402 (Hewlett-Packard, Palo Alto, CA) packed column GC, challenging my glass blowing expertise. We managed to build a well functioning GC/MS system, first with a homemade glass jet-separator, and later with the use of a Biemann–Watson-type all glass double stage molecular effusion separator provided by Varian MAT. Our all-glass interface had short heated connections which caused minimal thermal and no metal catalyzed analyte degradation and produced virtually identical cholesterol spectra in both GC/MS and direct inlet modes of operation. At that time this test became a widely used criterion for the satisfactory performance of contemporary GC/MS interfaces.

The GC/MS system greatly expanded our analytical capabilities by allowing direct analysis of mixtures, but it generated a large amount of spectral data, creating a serious data processing bottleneck. With both CH-4 and CH-7, like with most instruments of that period, data output was on oscillographic light-recorders and required manual counting of each peak on the photo-sensitive paper with the aid of a variable scale to compensate for the non-linear (square-root) scanning function of the magnet. For spectral data distribution to the submitting chemists, and for ease of record keeping, we had the light-recorded data manually plotted, usually by unemployed spouses of our staff. One advantage of the oscillographic recording was easy access to metastable peak information which we used to...
establish fragmentation sequences. Contemporary metastable peak studies were carried out mostly on double-focusing instruments for the detection of ions decomposing in the first or second field free regions of the flight path for “metastable maps” and other specialized applications. Interest in these measurements escalated during the 1969–73 period with the development of Ion Kinetic Energy Spectrometry (IKES) and Mass-Analyzed Ion Kinetic Energy Spectrometry (MIKES) techniques. The advent of fully computer operated instruments then led to the facile use of an assortment of preprogrammed “linked scan” and MS/MS functions for a variety of applications.

To take advantage of the rapidly evolving computer technology, Syntex had an early interest in developing computerized data processing. In the late 1960s, Syntex developed the first computerized single-crystal X-Ray crystallography system (model P1), commercialized it through a corporate division called Syntex Analytical Instruments, and later sold it to Siemens Analytical X-Ray Instruments. Around 1970 Syntex received an IBM-1800 computer on loan from IBM to encourage developments of its application in pharmaceutical research. Besides some simple instrument interfaces, we decided to use this computer to automate data processing from our CH-4 and CH-7 mass spectrometers.

During the second half of the 1960s, advances in commercially available computer technology led to reports of computerized data management, initially for handling the large amounts of data outputs from high resolution instruments. The pioneering work of D. Desiderio, K. Biemann and associates at Massachusetts Institute of Technology (MIT), for example, used a microdensitometer to digitize mass spectral data recorded on photoplates from a CEC 21-210B mass spectrograph and then processed the digitized data on an IBM-709 or IBM-360 computer achieving an impressive high mass-resolution data output (Desiderio & Mead, 1968). Similar advances were then reported by the research groups of A.L. Burlingame, Space Science Laboratory, University of California, F.W. McLafferty, Cornell University, R.M. Elliott and associates at AEI Ltd. and a few others. Without any available information about interfacing data output from a photomultiplier based magnetic sector instruments with an IBM-1800 computer, our endeavor required undertaking extensive hardware and software developments. We had to develop circuitries for an Analog to Digital Converter consisting of a signal amplifier for noise reduction, logarithmic amplifier to increase dynamic range, and a track-and-hold amplifier for the 16-bit analog to digital converter. Challenges in software developments included mass assignments for the peaks generated by the non-linear (square-root function) output of the magnet power-supply, and corrections for hysteresis of the magnet during repetitive scanning and for the differences in the mass defects of the analytes versus the perfluorokerosene or perfluoroeicosane calibration standards. These tasks were successfully accomplished by an in-house team, headed by Dr. Lewis Throop and consisting of James Work electronic engineer and William Morgenstern software engineer, before such data processing systems became commercially available as retrofits for magnetic sector instruments. Our data output provided barographic plots of the mass assigned peaks, with a possibility for regional signal amplifications, and a plot of the total-ion current versus sample evaporation time. In direct inlet mode the total-ion current plot allowed detection of multiple components of differing volatility, and in GC/MS mode it provided a universal GC trace to compliment UV recordings.

Our computerized data processing developments were of interest to instrument manufacturers as in the 1970s such software systems began to emerge as commercial accessories, notably for the Finnigan (San Jose, CA) and Hewlett-Packard quadrupole based instruments. Finnigan Corporation, a leader in this field, had a shared history with Syntex dating back to its founding days in 1966 (Chu & Finnigan, 1998). Syntex was interested in the evolving quadrupole technology and during a failed attempt to acquire a subsidiary of Electronic Associates, Inc. in Palo Alto, a manufacturer of residual gas analyzers, the negotiating executives struck a friendly relationship with Robert (Bob) Finnigan who was interested in applying this technology to develop a dedicated GC/MS system. Syntex was supportive of his endeavor and some executive members of the Corporation provided seeding financial and managerial help to establish Bob Finnigan’s company. The resulting Finnigan Corporation then proceeded to develop a quadrupole based GC/MS system as an independent company. We had been following closely their development efforts and provided occasional technical consultation. A pivotal advance in their developments occurred when Finnigan delivered its first instrument to a Syntex affiliate, Nobel Laureate Professor Joshua Lederberg at Stanford University Medical School. With their technical expertise and available resources, the Lederberg group computerized control of this instrument which resulted in a major improvement in its operation. This prompted Finnigan to search for means of acquiring computerization capabilities and with the alliance of a local startup company, System Industries in Milpitas, developed the first commercial computer control accessory for GC/MS. Subsequently, to attain manufacturing independence and to allow proprietary data system developments, Finnigan acquired two local companies, Quanta Matrix in Santa Clara and then INCOS in Berkeley. The INCOS data system allowed Finnigan to commercialize a state-of-the-art fully computerized quadrupole based GC/MS system, and then proceeded to market INCOS as a packaged data processing accessory adaptable to magnetic sector instruments. Our laboratory served as a beta testing site for one of their early model GC/MS systems.

By the 1970s and ‘80s our MS group gained full recognition as an essential core facility for the Corporation. Being part of a pharmaceutical research organization, selection of instrumentation to expand our MS capabilities had to be geared to provide the most efficient services relevant to our corporate needs for the investments involved. We couldn’t justify acquisition of the most advanced or sophisticated research grade instruments which were of interest primarily in academic research. When we needed any special MS support, we could enlist the services of the NIH-supported Biomedical Mass Spectrometry Resource at the University of California, San Francisco, as a regional supporter of their grant applications for newer instrumentations.

In 1976 we purchased our first medium resolution (20,000 at 10% valley) tandem sector instrument, the Varian MAT 311A GC/MS system with a reverse Nier-Johnson (BE) analyzer. This instrument came with a Varian 2740 gas chromatograph, all glass jet carrier gas separator and a DEC PDP-8 based (Digital Equipment Corporation, Maynard, MA) SS-100 data system. In 1978 we implemented several upgrades including the installation of a PDP-11 based SS-200 data system and a Varian 3700 gas chromatograph with a Biemann-Watson-type all glass separator. This instrument provided EI, CI and later field desorption (FD) and desorption chemical ionization.
(DCI) modes of operation, extending our services capabilities to the analysis of low volatility or fragmentation-prone compounds as well as to ion-kinetic-energy studies.

By this time MS having been recognized as an essential tool in pharmaceutical research, we had to significantly increase our instrumental resources to meet the ever increasing demand for our services. The growing demand for ADME (Absorption, Distribution, Metabolism and Excretion) related pharmacokinetic analyses prompted us in 1977 to purchase our first quadrupole GC/MS system, the computerized Finnigan 3200. Normally, this instrument was operated in EI mode but by substituting methane for GC carrier gas we could also use it for CI. In 1980 we purchased another small computerized GC/MS system with EI and CI capabilities, the unit resolution Varian MAT 112S tandem (BE) magnetic sector instrument. This instrument came with both GC interface and various direct inlet probes and was frequently used for DCI service. Since these instruments came partially or fully computerized and with a variety of accessories for different modes of operation, we had no further need for in-house instrument modifications and we just focused on their most efficient use.

In the early 1980s we encountered a need for high sensitivity and specificity GC/MS analysis of a large number of environmental samples (see Section IV(C) for details). For low resolution measurements we purchased our first bench-top GC/MS from Hewlett Packard (Palo Alto, CA), the HP-5970 mass selective detector coupled to a HP-5790A gas chromatograph. The operation of this instrument was computerized but data processing still required a remote computer. For high resolution analyses, in 1984 we acquired a fully computerized reverse Nier-Johnson geometry based Finnigan MAT 8230 mass spectrometer interfaced to a Varian 3700 gas chromatograph. Both of these instruments came equipped with high capacity turbomolecular pumps and with the use of low-flowrate capillary GC columns the effluents could be fed directly into the mass spectrometers without carrier gas separators. The MAT 8230 was a sophisticated high resolution instrument and with its SS-300 data system it offered a variety of pre-programmed linked scan MS/MS functions. We used this instrument for both GC/MS and direct inlet analyses in EI, CI, DCI and LSIMS modes of operation. In 1989 we increased its direct inlet throughput by installing a 46-sample AUDEVAP autosampler provided by Finnigan MAT. This accessory facilitated unattended day-and-night operation for direct inlet EI and CI analyses and proved to be quite reliable once carefully aligned.

Introduction of fast atom bombardment (FAB) in 1981 was a major breakthrough for extending MS to non-volatile compounds. It was then followed by the introduction of liquid secondary ion MS (LSIMS) and LC/MS systems using thermospray (TS) and electrospray ionizations (ESI). In 1988 we purchased our first triple quadrupole LC/MS system, the fully computerized Finnigan TSQ-70. This instrument came with thermospray LC/MS interface which we replaced by ESI and added FAB and then LSIMS capabilities. In 1987 Dr. Kenneth Straub joined our MS group and with his expertise in biopolymer analysis this instrument opened the door to services for oligopeptide and protein analyses. As an indication of the ruggedness and reliability of these modern instruments it is noteworthy that after the 1989 Loma Prieta earthquake, which rendered our research building uninhabitable, when we rolled this instrument into an adjacent facility it continued to provide unimpaired services.

With these developments, sequencing information of biopolymers became a high priority need at Syntex. To implement high energy collision MS/MS, combined with high mass resolution capability, in 1993 we purchased a fully computerized Kratos CONCEPT-HQ (Manchester, UK) hybrid (EBQQ) GC-MS/MS system. But when a partially computerized version was installed on a temporary basis, using a Sun Microsystems (Santa Clara, CA) 32 bit graphics workstation, Kratos discontinued its magnetic sector instrument business. Regrettably, we had to return this impressive instrument because Kratos could not guarantee completion of the fully computerized system and continued long term technical support. The Kratos instrument was replaced next year with another high resolution hybrid instrument, the fully computerized VG Fisons ZabSpec-Q/FPD GC-MS/MS system (Manchester, UK). This instrument consisted of an EBEQ analyzer with a microchannel focal plane detector after the second electric sector, and a DEC Alpha (Open VMS) workstation. In addition to the standard EI and CI capabilities, it provided LSIMS, flow-LSIMS and low as well as high energy collision MS/MS services for a wide variety of analyte types. This was our last investment in such large instruments which required a large laboratory floor space and the installation of an anti-vibration platform for its analyzer. Advances in compact tandem quadrupole and ion-trap technologies offered cheaper and more efficient instrumentation for biopolymer analyses. Our next acquisitions included two Finnigan TSQ-700 triple quadrupole LC/MS systems with ESI and atmospheric pressure chemical ionization (APCI) capabilities dedicated to peptide, protein and pharmacokinetic analyses. During this period we also linked the data stations of all mass spectrometers via Ethernet to a DEC VAX computer based Laboratory Information Management System (LIMS) to generate sample lists and to facilitate shared access to analytical results.

By the 1990s, increasing demands for pharmacokinetic studies and in-depth investigation of the biochemistry and biology involved with the targeted treatments became integral parts of modern pharmaceutical research. Simultaneously, dramatic advances in computer technology spurred the rapid development of smaller and more efficient instruments, featuring increased levels of automation and sophistication. At Syntex we followed the industry wide prevailing trend and acquired in rapid succession several self-standing and bench top quadrupole and ion trap based instruments mostly in support of bioanalytical needs. Instrument control and data processing with these instruments became so highly automated and reliable that their operation no longer required special MS expertise and could be used as routine “black box” instruments. Presently, users can load the autosampler of these instruments and then watch the analytical results on an attached or remote computer terminal which can also provide data interpretation as needed.

We came a long way with popularizing mass spectrometry as it evolved to become an essential tool for tackling previously intractable tasks. But it still remains a fascinating field for researchers interested in fundamental studies and in stretching its potentials by miniaturization, improving instrument performance and developing hitherto unimaginable applications in fields like biology, forensic science, cosmology, surgery rooms, etc.
B. Applications for Structural Elucidations

Our MS and NMR groups, in close cooperation, provided spectral and structure elucidation services as corporate core facilities. All research compounds synthesized or isolated within Syntex Research had been analyzed by our staff, and since we provided spectral interpretation whenever it was needed, this mode of operation proved most helpful for the submitting chemists as well as for our staff to develop wide ranging expertise in their fields. By retaining the original copies of all MS and NMR spectra we built an impressive library of reference spectra already in the 1970s. Our steroid mass spectral archives, which contained over a thousand interpreted spectra, gained widespread recognition and we frequently received requests for reference spectra or samples from researchers worldwide. The rapidly increasing non-steroidal spectral file had grown to contain over ten thousands spectra, but not having computerized spectral identification records, accessing specific spectra was cumbersome with the use of mainly logbook information. Unfortunately, we couldn’t take advantage of offers by organizations which commercialized spectral data files for coding our spectral identification records, accessing specific spectra was cumbersome with the use of mainly logbook information. Our files contained a significant portion of proprietary data and we lacked manpower for sorting them out.

The bulk of our structural elucidation work was in support of Syntex Research and when our contributions proved pivotal to certain projects we frequently collaborated in joint publications. These publications included numerous metabolite identifications, unexpected products from syntheses, identification of novel biologics (prostaglandins, peptides, etc.) and other projects, too many to cite in this recital. In addition to these in-house projects, we also received requests for help, or collaboration with projects involving structure elucidation tasks from academia and research institutes of every continent having such facilities.

As part of my employment agreement with Syntex I was allowed to pursue some extra-curricular research, not exceeding 10% of my workload. Benefiting Syntex, the resulting publications contributed to the scientific recognition of the Company. As other tangible benefits, it allowed our staff to partake in the excitement of doing publishable research besides just providing routine analytical service, and it proved helpful with recruiting and retaining the best candidates for our staff. The collaborative projects varied from limited involvements to some which led to noteworthy scientific contributions. For the sake of brevity, I omit discussion of most of these research projects which resulted in joint publications but have no redeeming value in the history of mass spectrometry, and present only two illustrative examples.

Initial request for sporation were spurred mostly by our expertise in the steroid field, but with time it expanded to sapogenins, alkaloids, prostaglandins and other fields too. During the late 1960s and throughout the 1970s, a collaboration with Professor G. A. D. Haslewood and his research team at Guy’s Hospital Medical School in London, UK developed into a productive teamwork leading to a dozen joint publications. The objective of these investigations was the study of the evolutionary development of bile mechanisms in vertebrates and our part of the work was the structure identification of bile alcohols and bile acids. The samples were hydrolysis products of bile salts and conjugates isolated from a large variety of marine and terrestrial species. Direct inlet and GC/MS analysis of acetyl and silyl derivatives proved essential for these investigations as the isolated samples or mixtures were often available only in a few milligram or sub-milligram quantities. Aided by our extensive spectral library of steroidal model compounds and our expertise in correlating fragmentation characteristics with oxidation patterns and stereochemistry, we were able to identify a number of bile constituents.

The evolutionary hypothesis of bile mechanism in all vertebrates starts with liver enzyme conversion of cholesterol (33) to C27 bile alcohols, then to C27 bile acids, and ultimately to side chain reduced cholic acid (69) and its analogs in more advanced species (Anderson et al., 1980). Our investigations of a wide range of evolutionarily primitive to advanced species contributed several key elements to this evolutionary scheme. Examples of the plethora of bile constituents we have identified are tabulated below.

**5α-Series**
- 56, 3β,7α,12α,26,27-pentol (latimerol)
- 57, 3α,7α,12α,25α,26-pentol (5α-bufol)
- 58, 3α,7α,12α,26,27-pentol (5α-cyprinol)
- 59, 3α,7α,12α,26-tetrol (deoxy-5α-cyprinol)
- 60, 3α,7α,12α,24β,26-pentol (5α-chimaerol)
- 61, 3β,7α,16α,26-tetrol (myxanol)
- 62, 3β,7α,26-triol (deoxyxyminol)

**5β-Series**
- 63, 2β,3α,7α,12α,26-pentol (arpaimol-A)
- 64, 2β,3α,7α,12α,26,27-hexol (arpaimol-B)

**5β-Series**
- 65, 2α,3α,7α,12α-tetrol (arpaimic acid)
- 66, 3α,12α,22β-triol
- 67, 3α,7α,12α,22β-tetrol

**5α-Series**
- 68, 3α,7α,12α,24-tetrol (petromyzonol)

**5β-Series**
- 69, 3α,7α,12α-triol (cholic acid)

Substitution assignments to C26 versus C27 positions are not meant to indicate stereochemistry at C25.

In close agreement with the hypothetical evolutionary scheme, living descendents of the most evolutionarily senescent species we have examined yielded the most primitive C27 or C26 bile alcohols and bile acids in both 5α- and 5β-configurations as their predominant bile constituents. Examples include latimerol (56) from coelacanth Latimeria chalumnae; 5α-bufol (57), 5α-cyprinol (58), deoxy-5α-cyprinol (59) and
5α-chimaerol (60) from 3 different lung fish from South America, *Lepidosiren paradoxa*, Australia, *Neoceratodus forsteri* and Africa, *Protopus s. aethiopicus* (Amos et al., 1977); 5α-chimaerol (60) from the sucker fish *Catostomus commersoni* (Tokés, 1970); myxiniol (61) (Anderson et al., 1967) and deoxymyxiniol (62) (Tokés, 1969) from the jawless hagfish *Myxine glutinosa*; arapaimol-A (63) and -B (64) and arapaimic acid (65) from the large freshwater fish *Arapaima gigas* (Haslewood & Tokés, 1972); tri- and tetrahydroxy coprostanoic acids (66 and 67) from the green turtle *Chelonia mydas* (Haslewood et al., 1978) and petromyzonol (68) form jawless lamprey *Pertomyzon marinus* (Haslewood & Tokés, 1969).

Bile constituent profiles often show good correlation with the phylogenetic classification of related species and we called attention to their possible value as a molecular parameter in taxonomic evaluations. A pertinent example was encountered during the survey of bile constituents from 29 frog species from Nigeria (Anderson et al., 1974). Significant molecular diversity was prevalent in these species but the presence of certain signature bile alcohols provided good differentiation between the *Rana*, *Bufo* and other genera, and pointed to the need for reexamining the taxonomical classification of some outlying species. Such molecular parameters were the only biochemical aids for the taxonomists before the development of the currently used genetic profiling. These comparative studies, however, must be carried out on adult species because we have found considerable changes in bile alcohol profiles during the survey of bile constituents from 29 frog species from Nigeria (Anderson et al., 1974). Significant molecular diversity was prevalent in these species but the presence of certain signature bile alcohols provided good differentiation between the *Rana*, *Bufo* and other genera, and pointed to the need for reexamining the taxonomical classification of some outlying species. Such molecular parameters were the only biochemical aids for the taxonomists before the development of the currently used genetic profiling. These comparative studies, however, must be carried out on adult species because we have found considerable changes in bile salt profile during the tadpole to adult metamorphosis in *Rana catesbeiana* (Anderson et al., 1979).

Second example of a joint research project with outside collaborators involved a study with Professor David Feldman, at the Division of Endocrinology, Stanford University Medical School in the late 1980s. This project involved investigations of an estrogen binding protein discovered in the yeast, *Saccharomyces cerevisiae*. During screenings for a ligand for this protein the Stanford group encountered a persistent contaminant in their experiments with a protein-binding trace constituent which was suspected to originate from the sterilized polycarbonate containers. In 1992 we analyzed a trace amount of water residue from their autoclaved containers and identified this contaminant as the monomer of polycarbonate, bisphenol-A (BPA, 70) (Krishnan et al., 1993). In addition to the obvious problems this contaminant creates in the laboratory environment, our report also raised a warning to the general public of the potential health concerns this endocrine-disrupting compound may present leaching from the widely used polycarbonate containers commercialized under the Nalgene® trademark. This discovery led to subsequent changes in the manufacturing of Nalgene to eliminate BPA leaching, but the safety of BPA and related estrogenic contaminants in food containers remains a contested issue.

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Our involvements with these and many other joint research projects were made possible by the use of Syntex’s analytical instruments and the expertise of our staff. Every accomplishment was an exciting and gratifying experience for our staff and the power of mass spectrometry gained high esteem at Syntex Research.

### C. Quantitative Mass Spectrometry

Quantitative analytical needs in pharmaceutical research arise for various reasons but mass spectrometry usually plays a pivotal role when high sensitivity and/or high specificity is required. Coupling mass spectrometers with chromatographs, GC/MS, LC/MS, and to a lesser extent SFC/MS, revolutionized pharmacokinetics and became the backbone technologies in modern pharmaceutical research. These techniques play a pivotal role in the mandatory ADME (Absorption, Distribution, Metabolism and Excretion) preclinical studies and during the later phase clinical studies. By the mid 1970s our MS group had been involved almost continuously with pharmacokinetic and other quantitative analytical tasks, some of them requiring extensive and challenging method development efforts. For effective management of these tasks in 1980 we established a separate analytical group dedicated to bio-analytical and drug metabolism studies, GC/MS and LC/MS method developments became constant challenges for this group with every new compound selected for evaluation. These method developments, however, followed mostly standard procedures and I do not intend to discuss them in any detail.

Some of the truly challenging quantitation tasks we encountered at Syntex were not pharmacokinetics related tasks and required extensive method development efforts, pushing the boundaries of the state-of-the-art. Occasions for such tasks arose by the need for analytical support in company liability issues, troubleshooting manufacturing or quality control problems, environmental contamination issues and other cases. Examples of such occurrences will be illustrated by two cases, involving an environmental study and a regulatory requirement issue, as depicted below.

In 1969 Syntex bought Hoffman-Taff, Inc. in Verona, Missouri to expand into the animal feed business. Concurrently, part of the Hoffman-Taff facility was subleased to Northeastern Pharmaceutical and Chemical Company (NEPACCO) which during the Vietnam War produced the defoliant, Agent Orange, until 1972. NEPACCO hired a local company, IPC, for the disposal of its industrial byproducts and IPC in turn subcontracted this task to a waste hauler, Russell Bliss. In 1970 Bliss was also contracted by the city of Times Beach, not far from the Verona site, to oil its dusty roads with used motor oil. Unaware of the toxicity of the NEPACCO waste, Bliss mixed it with used motor oil and between 1971 and 1976 he sprayed it on several roads and farms in the Times Beach neighborhood, including his own front yard. Subsequent wide spread reports of animal deaths in these sprayed areas prompted an investigation for possible environmental contamination which revealed that the NEPACCO waste contained highly toxic chlorinated dioxins. Testing soil samples from these sites confirmed the presence of high-level toxic contaminations and led to the eventual complete evacuation of this city in the 1980s. This site became known as the Times Beach environmental disaster area, one of the Environmental Protection Agency (EPA) Superfund cleanup sites. As owner of the Verona plant, and the sole surviving company with financial resources, Syntex had to assume shared responsibility for the remediation process which necessitated the development of an ultra high sensitivity quantification method for the analysis of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, 71) in solid samples.

5α-chimaerol (60) from 3 different lung fish from South America, *Lepidosiren paradoxa*, Australia, *Neoceratodus forsteri* and Africa, *Protopus s. aethiopicus* (Amos et al., 1977); 5α-chimaerol (60) from the sucker fish *Catostomus commersoni* (Tokés, 1970); myxiniol (61) (Anderson et al., 1967) and deoxymyxiniol (62) (Tokés, 1969) from the jawless hagfish *Myxine glutinosa*; arapaimol-A (63) and -B (64) and arapaimic acid (65) from the large freshwater fish *Arapaima gigas* (Haslewood & Tokés, 1972); tri- and tetrahydroxy coprostanoic acids (66 and 67) from the green turtle *Chelonia mydas* (Haslewood et al., 1978) and petromyzonol (68) form jawless lamprey *Pertomyzon marinus* (Haslewood & Tokés, 1969).
Successful developments of these quantitation methods in those days remain respectable accomplishments even with today’s standards. However, these results were communicated only within Syntex and to certain government agencies, their public disclosure was discouraged by the company due to legal concerns and they never got published in any scientific journal.

V. SERVICES TO THE MASS SPECTROMETRY SOCIETY

I joined the American Society for Testing and Materials (ASTM) Committee E-14 in 1968 just before its Executive Committee decided to establish and incorporate the American Society for Mass Spectrometry (ASMS) as a professional organization. This way I joined ranks with the charter members of the society and continued my membership ever since. I found the programs of this society stimulating, having members representing a wide range of scientific disciplines. During the following decades I got involved with a variety of functions of the society, as speaker and Session Chairmen at conferences and as a member of various ASMS Committees. In addition to my ASMS activities I also organized and chaired mass spectrometry related symposia at the Pacific Conference on Chemistry and Spectroscopy series.

Having gained recognition of our expertise in a variety of disciplines at Syntex, I received frequent requests for reviewing papers submitted for publication from several different journals. I considered these refereeing requests important and interesting service, although occasionally rather time consuming tasks. I have been nominated twice by the ASMS Board of Directors for a Board position, first in 1985 together with Charles McEwen of DuPont Company and then in 1996 with Michael Story, co-founder of Finnigan Corporation. Both times my most worthy opponents won the election but it was an honor to be nominated to these positions. Two of my contributions which resulted in lasting consequences for the society were the co-founding and 12 year chairing of the Asilomar Conference of Mass Spectrometry (ACMS), and my involvement with the founding of the Bay Area Mass Spectrometry (BAMS), a regional mass spectrometry discussion group. Both of these organizations continue to be active and my involvements with them are discussed in some detail in the following sections.

A. Asilomar Conference on Mass Spectrometry

During the 1970s I attended various Gordon Research Conferences (GRC) and I found these meetings highly effective in promoting the in depth discussion of selected research topics. The relaxed and informal environment, mostly without any urban distractions, allowed unhindered concentration on the scientific agenda. The 1980 GRC meeting on Analytical Chemistry in New Hampshire included speakers on mass spectrometry. After that meeting I was convinced that this is the type of research conference which would be most helpful for promoting research discussions in mass spectrometry. I tried to arrange with the GRC organization the inclusion of a series of meetings dedicated to MS topics, but these efforts proved futile. An opportunity to pursue my plans arose in September 1980 when I attended a three-day “MS/MS Conference” at the Asilomar Conference Center in Pacific Grove, CA, organized by William F. Haddon, USDA Western Regional Research Center,
Albany, CA and J. Ronald Hass, NIEHS, Research Triangle, NC. This was a brief but very intense conference on a timely topic and in an environment which immediately appealed to me as the ideal setting for a GRC type conference series. After the conference I shared my vision with Bill Haddon and Ron Hass and Ron decided to join me in this endeavor.

‘Sporadic Gordon Research Conferences on MS topics had been organized during and after the late 1980s by ACMS attendees, Michael Bowers, University of California, Santa Barbara, CA and Jack Beauchamp, California Institute of Technology, Pasadena, CA but these meetings catered mostly to researchers interested in ion chemistry and related topics.

The Asilomar Conference Center was located on the beach at the scenic Pacific Grove area of Monterey Peninsula in California. It was designed during the period of 1913–1929 by the noted California architect Julia Morgan, originally to serve as a Young Women’s Christian Association (YWCA) retreat, but was later turned over to the California State Parks system with a requirement that it should retain its tranquil retreat style. The rustic rooms were devoid of telecommunication, radio or TV and in the 1980s most rooms were for shared occupancy. Asilomar provides three meals a day and a suitable conference room in a former chapel. For evening sessions or socializing there are convenient halls for gatherings and at midnight when the exhausted and some “high spirited” participants stroll back to their rooms they are often accompanied by deer or raccoons.

With Ron Hass’ help, I embarked on registering Asilomar Conference on Mass Spectrometry (ACMS) as a nonprofit professional organization and formulated our operating policies. Regular coverage of the full scope of mass spectrometric topics had been achieved already at both domestic and international levels by the annual ASMS conferences and the triennial International Conference on Mass Spectrometry (ICMS). We designated ACMS to complement these conferences by small scale international meetings, dedicated to the in-depth discussion of the most recent developments in selected topics, aiming to stimulate new research ideas in these fields. All oral and poster presentations were by invitation, covering the most seminal research in the selected fields worldwide. Attendance was limited to 150 and the costs were kept to a minimum to facilitate this goal we disallowed wearing necktie during the conference.

Another aim of the conference was to provide a relaxed, informal setting that encourages uninhibited discussions between seasoned researchers as well as newcomers to the field. To facilitate this goal we disallowed wearing necktie during the conference. This was initially startling for some distinguished participants from Europe and Asia, but based on the departing comments by many participants, this move had its desired affect. As a colorful historical event, during the 5th ACMS in 1986 we encountered a need to enforce this no-necktie policy. Rising to the occasion, I had to “liberate” the unsuspecting Professor Keith Jennings, University of Warwick, UK, of his treasured silk necktie (he forgot that he was wearing it when he returned to our banquet dinner from an off campus engagement). He suffered through this humiliation in a most gracious manner, but when he returned to a subsequent conference he paid me back with a hilarious roasting during the banquet dinner, an invitation for dinner at his home, and a Warwick University necktie to make sure I’ll be properly attired for the occasion. His mutilated necktie became a precious membrabilia and has been shown at subsequent conferences to deter any future noncompliance.

Other inventions we implemented to ease up the participants during their presentations included the use of a fishing rod as pointer (the small red laser pointers of the time were not always visible on colored slides), and we placed a small remote controlled chirping and tail-curling monkey perched over the podium as timer for the presentations. This monkey played a key role in securing adequate time allowance for discussions after each presentation. We considered these discussions an essential part of a stimulating research conference and in the program we allocated 10 min for this purpose after each presentation. However, some speakers considered this a contingency allowance for extended presentations and often Session Chairmen were too timid to timeout distinguished presentations. The monkey’s function was to give a gentle 5-minutes warning, and at the end of the time allotment it announced in no uncertain terms that he had enough of listening to lengthy sermons in this chapel (our conference room). This monkey had a dramatic improvement on adherence to time allocations and it was amusing to see how certain speakers bargained for extra minutes —while Fred McLafferty of Cornell University stopped his presentation in the middle of a sentence, Peter Roepstorff of Odense University, Denmark, came prepared to bribe the monkey with a banana.

The first meeting which was actually called Asilomar Conference on Mass Spectrometry was in 1981, but to acknowledge that in the previous year the MS/MS Conference took place at this site we called it the 2nd ACMS of this series. This, and our decision to skip every third year to avoid competition with the European triennial ICMS meetings, created some confusion for the uninitiated but at the time we felt that these moves were well justified. Being an initially unknown conference, starting this series required surmounting a number of obstacles. We considered enlisting the participation of the most distinguished contributors of the selected topics worldwide of foremost importance and to accomplish this without being able to offer any financial compensation was a major challenge. This we accomplished by raising the standards of invitations to such high levels that the invited speakers felt compelled to participate. With some key contributors we also had to encourage instrument manufacturers to provide travel grants for their favorite customers. Another challenge was providing accommodations for
visitors from all over the world in a rustic facility, offering mostly shared bedrooms and only a few single occupancy rooms which had shared bathrooms. It was gratifying to learn that most participants managed to overcome these inconveniences and became enthusiastic supporters of the conference. Reflecting on their congeniality, they even forgave their absentminded neighbors when they kept locking each other out of their shared bathrooms.

Since the 1980s, the facilities of the Asilomar Conference Center have been gradually upgraded and modernized, now offering W-Fi service, bathrooms with every room and sharing bedrooms is no longer a requirement for attendance. ACMS has also evolved as a more conventional ASMS affiliated annual conference, which allowed the elimination of some initial organizational constraints, but it managed to retain much of its original character and remained a high quality international research conference series.

The events of the first ten ACMS meetings are summarized in Table 1. The 2nd ACMS meeting in 1981 on the topic “High Resolution Mass Spectrometry and MS/MS” was a resounding success with full house attendance and substantial international participation. We received strong encouragement from the participants to continue with the organization of this series. Learning from the level of interest in participation, we extended the 3rd ACMS in 1983 to a four day meeting and ventured into a less popular but highly research oriented topic, “Structure Identification of Gaseous Ions.” As expected, the attendance was slightly lower but the conference was acclaimed highly successful by the participants. The speakers included most of the prominent North American and international researchers in this field and we also introduced younger evolving key contributors, Helmut Schwarz, Technische Universität, Berlin, and Leo Radom, Australian National University, Canberra.

The 4th ACMS was shifted to February 1985 to avoid overlap with a Biomedical Mass Spectrometry Conference in San Francisco in the fall of 1984 and then had to be cancelled due to a subsequent overlap with a rescheduled Pittsburgh Conference. However, the 5th ACMS in 1986 on “New Developments in Mass Analyzers” was again an unqualified success (Tókés, 1987). With nearly full house attendance and participants from four continents and nine countries the program covered new developments and discussions of the relative merits of magnetic sector, FT-MS, time-of-flight, quadrupole, ion trap, multi sector and hybrid analyzers, as well as the Wien Filter and energy analyzer systems. Of the three plenary lectures by Hisashi Matsuda, Osaka University, Japan, Curt Brunnée, Finnigan MAT, Germany, and R. Graham Cooks, Purdue University, the opening lecture by Brunnée, entitled “The Ideal Mass Analyzer—Fact or Fiction,” was such a stunning presentation that upon demand by the audience he submitted it for publication in the International Journal of Mass Spectrometry and Ion Processes where a separate issue was devoted to this presentation (Brunnée, 1987) (Fig. 5).

By 1986, we realized that continuation of this series at the high level of expectations, it was necessary to establish a formal organizing committee and to appoint key contributors in specific fields to serve as program chairs. It also became evident that since both ACMS and ASMS were serving the same community, merger of these organizations would help the coordination of our activities and would help to ensure longevity of the ACMS series. After lengthy negotiations with ASMS Presidents Graham Cooks, followed by Gerry Meisels, in 1987 we signed a merger agreement with ASMS which became effective in January 1, 1988. At this stage coordinating our efforts with ASMS became especially important because during the 5th ACMS meeting, participants Kenneth Bush, Robert Cotter and Mark Ross decided to start a parallel ASMS affiliated research conference series on the East Coast at the Sanibel Resort in Florida. Starting in 1988 this became the ASMS affiliated Sanibel Conference series.

The newly formed ACMS organization consisted of a 5 member Board of Directors (chairman, 2 organizers and 2 ASMS representatives) and an invited Program Chairman. This arrangement brought aboard Gary L. Glish and Graham Cooks from the ASMS side and led to a subsequent 5-year service by Graham Cooks on the ACMS Board. The first invited Program Chairman was Michael Gross, University of Nebraska, for the 6th ACMS meeting in 1987 on “Fundamentals of Ion Activation, Collisions, Photons and Reactions with Metal Ions.” This and the following 7th ACMS in 1989, with Christie G. Enke, Michigan State University as Program Chairman on the topic of “The Role of Computers in Modern Mass Spectrometry,” both turned out highly stimulating and well attended meetings. In fact, with the 7th ACMS we had our first encounter with an overload of applicants. By this time ACMS became an internationally recognized, high quality meeting which led to new challenges—we had more participants with important research contributions, deserving oral presentations, then we could accommodate. Some of these illustrious contributions had to be shifted to poster presentations and to provide proper emphasis on their importance at the 9th and subsequent meetings a special oral session was implemented where all poster presenters were given 5 min to summarize the highlights of their presentations.

In line with the international nature of these conferences, for the 8th ACMS on “Intermediates in Gas-Phase Ion Chemistry” we invited a European program chairman, Helmut Schwarz, Technische Universität, Berlin. For the 9th ACMS on “Trapped Ions: Principles, Instrumentation and Application,” we invited for the first time two program chairmen, R. Graham Cooks and Alan G. Marshall, The Ohio State University. Both of these were again highly stimulating and well attended meetings with forty percent of the oral presentations by international speakers. For the 8th ACMS we added to the program a surprise bonus lecture by Nobel Laureate Professor Yuan T. Lee, University of California, Berkeley. With the aid of Soros Foundation for travel grants, we began getting contributors from Russia for the 9th and 10th ACMS meetings (Fig. 6).

Organizing the 10th ACMS in 1993, however, turned out to be a major challenge. Due to overbooking, the Asilomar Conference Center couldn’t provide us the facilities we considered essential. Finding a suitable alternative facility on short notice was very difficult and we ended up moving this conference to The Aspen Lodge in Estes Park, Colorado. Instead of the Pacific Ocean, the Colorado Rocky Mountains provided a spectacular panoramic setting for this conference but the high altitude at this facility, being at 9,100 ft elevation, was of some concern. The topic of this conference was “Time-of-Flight Mass Spectrometry” and with Kenneth Standing, University of Manitoba, Canada, as Program Chairman we put together a truly stimulating program. We had again a strong international participation, including most key contributors from Europe,
| Conference & Dates | Program Chairmen | Organizers, Board Members, Chairman | Topic |
|-------------------|------------------|------------------------------------|-------|
| MS/MS Conference* Sept. 21-24, 1980 | W.F. Haddon J.R. Hass | W.F. Haddon J.R. Hass | MS/MS |
| 2nd ACMS Sept. 2-5, 1981 | L. Tőkés J.R. Hass | J.R Hass L. Tőkés | Recent developments in High Sensitivity Mass Spectrometry and MS/MS |
| 3rd ACMS Sept. 18-22, 1983 | L. Tőkés | W.H. Haddon J.R. Hass L. Tőkés | Structure Identification of Gaseous Ions |
| 4th ACMS** Feb. 24-28, 1985 | J.R. Hass | W.H. Haddon J.R. Hass L. Tőkés | Production of Ions from Surfaces |
| 5th ACMS Sept. 28-Oct. 2, 1986 | L. Tőkés | A.M. Falick J.R. Hass L. Tőkés | New Developments in Mass Analyzers |
| 6th ACMS Oct. 11-15, 1987 | M.L. Gross R.G. Cooks A.M. Falick G.L. Glish J.R. Hass | L. Tőkés | Fundamentals of Ion Activation: Collisions, Photons and Reactions with Metal Ions |
| 7th ACMS Sept. 24-28, 1989 | C.G. Enke A.M. Falick G.L. Glish J.R. Hass R.C. Murphy L. Tőkés | | The Role of Computers in Modern Mass Spectrometry |
| 8th ACMS Sept. 23-27, 1990 | H. Schwarz V.M. Bierbaum A.M. Falick A.G. Marshall R.C. Murphy L. Tőkés | | Intermediates in Gas Phase Ion Chemistry |
| 9th ACMS Sept. 27-Oct. 1, 1992 | R.G. Cooks A.G. Marshall | R.C. Cooks A.M. Falick A.G. Marshall R.C. Murphy L. Tőkés | Trapped Ions: Principles, Instrumentation and Applications |
| 10th ACMS Oct. 3-7, 1993 | K.G. Standing A.G. Marshall R.C. Murphy L. Tőkés | R.G. Cooks A.M. Falick | Time-of-Flight Mass Spectrometry |

*This conference was not an ACMS meeting but we accredited it as the 1st in this series to acknowledge that it took place at Asilomar in 1980.

**The 4th ACMS was scheduled for February 1985 to avoid overlap with a Biomedical Mass Spectrometry Conference in San Francisco in the fall of 1984, and then had to be cancelled due to a subsequent overlap resulting from a rescheduled Pittsburgh Conference.
Australia and Canada, inciting spirited discussions of novel proposals. Fortunately, there were no problems with altitude sickness and the always unpredictable snowing at this elevation didn’t start until the day after the conference. Metaphorically speaking, this conference was now brought to “new heights” and it became time for me to step aside and let the Board of Directors continue the management of ACMS which at this point was already a well established and highly respected organization. My continued involvement with the next two to three ACMS meetings was only at a consulting level (Fig. 7).

Overlooking organization related agonies, this 12 year involvement with ACMS between 1981 and 1993 was amongst the most exciting and rewarding times of my career. I owe a great deal of gratitude to my organizing partners, J. Ronald Hass (1st–8th ACMS), Arnold Falick (5th–11th ACMS), William F. Haddon (1st, 3rd, and 4th ACMS), to all those who joined us as Board members and program chairmen after our affiliation with ASMS, and to all other participating colleagues and friends worldwide whose contributions have been crucial to the success of this endeavor.

B. Bay Area Mass Spectrometry

By the end of the 1970s, with the presence of Finnigan, Hewlett-Packard and Varian corporate headquarters, representative offices of other instrument manufacturers, and several prominent academic and industrial users of MS, the San Francisco Bay Area became a vibrant center of mass spectrometry related activities. To facilitate information exchange by the local practitioners and to tap into the vast intellectual resource of visiting scientists coming to the Bay Area, in 1980 Brenda Kimble, University of California, Davis, began organizing periodic dinner lecture meetings at various locations. These meetings became quite popular since they offered an opportunity for staff members of both instrument users and manufacturers, who normally can’t attend national or international conferences, to meet their colleagues and share experiences. By 1981, it became obvious that to ensure continuance of these meetings a more structured organization was needed to help and ultimately relieve Brenda of the organizational burdens. I was an ardent supporter of these meetings and participated in setting up an organizational structure, consisting of a four-member elected Executive Committee (chairman, chairman-elect, treasurer and secretary), prepared bylaws and registered “Bay Area Mass Spectrometry” (BAMS) as a non-profit organization. In 1982 I became the first elected committee member to serve a two year term as Chairman-Elect and then Chairman of BAMS. (In 1982 Brenda was appointed to serve as the first Chairman to acknowledge her prior organizational services, which at that point became the responsibility of the Chairman-Elect.)

BAMS continued to gain momentum in the 1980s with regular monthly meetings, attendance ranging from 60s to 90s and with prominent speakers to over 100 participants. It became one of the most active regional mass spectrometry discussion groups in North America and remains active to this date.
VI. EPILOGUE

Having started in the days of manual typewriters, sliderules for calculations and variable scales for mass assignment of spectral peaks, it has been fascinating to follow the development of modern mass spectrometry. While I was actively involved in this field, mass spectrometry has evolved from a novelty technique to an essential tool in pharmaceutical research. During my close to three decades tenure at Syntex, my responsibilities had been extended to include supervision of all instrumental analysis and electronic design services, and management of such a large department demanded my full attention. I always strived to attract staff members who were genuinely interested in their selected field and this way we managed to build a highly competent team of analytical chemists. Not being an educational institution, our mass spectrometry group had only limited opportunities for basic research, but I used every opportunity to promote the professional growth of our staff. Many of our staff members who started or pursued their career in our group have gained expertise which proved helpful in their subsequent career development, in some cases leading to professor position in academia and Department Head, Vice President and President level positions in the corporate environment. As a community service, during the summer months we offered internship positions to college students. Invariably these candidates found their exposure to pharmaceutical research stimulating and highly educational experience, prompting many of them to select chemistry as their field of interest.

In 1994, after Syntex was acquired by Roche Holding Company, my tasks in the Institute of Analytical Research changed to the management of down-sizing our operations, that is, to deconstruct the highly proficient organization which I helped to build for 28 years. Since this was no longer an attractive career objective for me, I accept an offer for early retirement (with admittedly generous severance benefits) and left Syntex in January 1995.

One stipulation in retaining my retirement benefits was that I do not seek industrial employment for 2 years. This didn’t prevent me from continuing my scientific work as an independent consultant and for the following 10 years I continued working with about a dozen different pharmaceutical research and analytical service organizations. However, no longer being involved with any personal research project, it was increasingly difficult to stay abreast with the rapidly changing analytical technologies and in 2005 I terminated my technical consultations and focused entirely on management issues. It was difficult to leave a career in mass spectrometry which fascinated me throughout my professional life and to cease relationships with the many friends and colleagues all over the world. It was an emotional experience to read some of my correspondence with these individuals during the preparation of this review article.

I am indebted to Syntex management for providing an inspiring working environment during my tenure with the company, and to the many colleagues at Syntex Analytical Research who shared my dedication to excellence, even while facing occasional frustrating instrument failures. I wish to express my gratitude to my colleagues in the MS and NMR groups for their strive to stay in the frontline of their fields, and my special thanks to all those at Syntex Research who were willing to exert extra efforts by participating in extracurricular research projects besides their company related responsibilities. In the MS group, in
addition to the individuals mentioned already in Sections III and IV, I wish to acknowledge the significant contributions with special projects of Bernard Amos, Diane Cho, Larry Lightman, Hans Schäuren, and Drs. Ian Massey and Kelvin Chan. I also wish to thank Dr. William Fitch for his help with preparing the illustrations of this article.

During my cursory discussions of historical developments, the lists of key contributors often include the term “and others.” My apologies for omitting individual recognition of many significant contributors but this reminiscing recital was not meant to provide detailed historical survey of any particular developments in mass spectrometry.

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