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Mass Spectrometry

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OVERVIEW

In a previous issue of this review (*A3*), it was stressed that mass spectrometry covers an enormous field when judged in terms of the variety of interests encompassed. During the two years which have since elapsed, the number of activities which employ mass spectrometry as an analytical or purely scientific tool have continued to proliferate. Fields of application include biomedicine, environmental studies, toxicology, entomology, geochemistry, biochemistry, and organic, organometallic, and inorganic chemistry. In pure mass spectrometry, research may vary widely from, e.g., the study of ion/molecule processes between atomic species through to the investigation of the structure of steroid cations in the gas phase. Perhaps the most eye-catching of the recent activities in mass spectrometry has been the use of double-focusing gas chromatograph–mass spectrometers in the Viking Lander missions to Mars (*A1*, *A5*). This impressive range of interests in mass spectrometry, therefore, requires a variety of inlet systems, ion-source types, mass analyzers, mass ranges, mass resolutions, and data systems. It is this proliferation of techniques that has led to the situation where it not always easy to select the most appropriate method(s) from the sometimes exaggerated claims in the literature and from instrument companies.

In order to explore the interdisciplinary potentialities and reap the certain benefits of many innovative instrumental concepts, techniques, and combinations within present reach, it is of central importance to foster purposefully (*A6*) the design and manufacture of highest sensitivity, high performance mass spectrometers as well as to enjoy the presently more economically fruitful quadrupole explosion for routine analytical applications. Attention to improvement of ion optics and manufacturing techniques, mechanical and electrical stability, microprocessor utilization, multichannel arrays and a host of other considerations would permit a new thrust for research into the subnanogram to subpicogram levels of biomolecular and environmental organic chemistry.

One of the main advantages of mass spectrometry over other spectroscopic techniques is its sensitivity. The detection limit for mass spectrometry in organic analysis is undoubtedly lower than that for NMR and IR, despite the application of Fourier transform techniques to enhance the data in these two areas. "Sensitivity" is difficult to quantify, but it is possible on some instruments to obtain full mass spectra on 1 ng of material in about a second. The detection limit is several orders of magnitude lower using ion monitoring techniques. Another asset of mass spectrometry is its capability in handling complex mixtures, currently via GC/MS (*A2*) and high resolution gas chromatograph/high resolution mass spectrometry (*D37*) and in future applications via the complementary techniques, LC/MS (*A1a*) and CID analysis (*Q35*, *Q39*), which are proving particularly suitable for separation and analysis of underivatized and insoluble compounds. Compounds now amenable to mass spectrometry vary from low molecular-weight gas mixtures to high molecular-weight (>mass 3000) natural products (*C41*, *C53*, *C54*). Quantitative analysis is available where required. Various ionization techniques are used to provide complementary structural information and molecular weight and elemental composition data are readily obtainable. Stereochemical information is becoming increasingly available from organic mass spectrometric techniques (*F13*), although of course at a shallower level compared with NMR. One advantage of mass spectra is the suitability for data storage and library retrieval, since the positions (masses) of the peaks in the spectrum of a given compound are fixed (cf., solvent effects on chemical shifts in PMR spectroscopy). One disadvantage of the technique is that it is destructive (unlike NMR, IR, UV).

The nomenclature employed in mass spectrometry was described in the last issue of this review (*A3*) as being vague,

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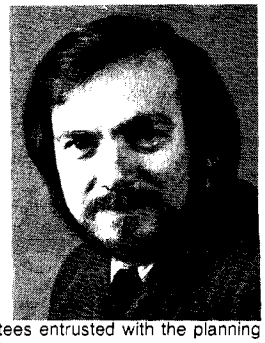

A. L. Burlingame is currently research chemist and director of the NIH-supported National Biomedical, Clinical Mass Spectrometry Resource and related interdisciplinary research programs at Space Sciences Laboratory, University of California, Berkeley. He received his B.S. from the University of Rhode Island and his Ph.D. from the Massachusetts Institute of Technology in 1962 with K. Biemann. He immediately joined the staffs of the Department of Chemistry and Space Sciences Laboratory and was assistant professor of chemistry until 1968. He became associate research chemist in 1968 and research chemist in 1972. From 1964 to 1973, he was a member of several interdisciplinary scientific teams and committees entrusted with the planning and conduct of the lunar science program, and the preliminary examination and distribution of lunar samples from the U.S. Apollo and U.S.S.R. Luna sample return missions. During this time he poineered the development of real-time, high sensitivity, high resolution mass spectrometry; field ionization kinetics and deuterium-difference spectroscopy in NMR. During 1970–1972, he was awarded a J. S. Guggenheim Memorial Fellowship which was spent on biochemical-biomedical applications of mass spectrometry with J. Sjövall at the Karolinska Institute, Stockholm. Since that time, interesting characterization of complex mixtures of biological and environmental substances related to human health has led to development of combined high resolution gas chromatography and real-time, high resolution mass spectrometry. Recent studies in chemical carcinogenesis have led to development of field desorption, collision-induced decomposition techniques for structure of such polyfunctional polar biological substances. His research interests lie in the development of computerized double-focusing mass spectrometry, field ionization kinetics, and Fourier transform ^{13}C.D nuclear magnetic resonance spectroscopy and their applications to biomedical and clinical research and organic ecochemistry.

Cedric Shackleton has been head of the Steroid Unit of the Division of Clinical Chemistry, Medical Research Council, Clinical Research Centre, Harrow, since 1969. He received his B.Sc. degree from the University of St. Andrews and his Ph.D. at the University of Edinburgh for a thesis reporting a study of peri-natal adrenal steroid synthesis. The award of a Royal Society Fellowship permitted him to study GC/MS techniques in steroid analysis with Professor Jan Sjövall in Stockholm during 1968–1969 and since this time he has been using the technique for steroid identification and quantification. While on leave from the Medical Research Council in 1972–1973, he was a World Health Organization consultant in steroid analysis to the University of Isfahan, Iran, and in 1976–1977 he was assistant director of the Biomedical, Clinical Mass Spectrometry Resource, Space Sciences Laboratory, University of California, Berkeley. Because of his interest in the GC/MS diagnosis of steroid synthetic abnormalities in newborns and infants, he has recently been awarded senior lecturer status at the Institute of Child Health, University of London. In addition to his long term interest in peri-natal steroid synthesis, he has recently become involved with a study of the etiology of hypertension due to apparent mineralocorticoid excess. He is a member of the Society for Endocrinology (United Kingdom).

Ian Howe was educated at the University of Cambridge, gaining a Prize Scholarship in 1965 and his B.A. in Natural Sciences in 1966. He obtained his Ph.D. in 1969, for a thesis entitled "Substituent Effects in Organic Mass Spectrometry" under the supervision of Dr. D. H. Williams. It was during this period that he developed an interest in the application of fundamental theories to the formation and breakdown of gaseous organic ions, which forms the basis for his contribution to this review. He spent a year in Professor E. W. McLafferty's Laboratory at Cornell University in 1969–1970, working on isotope and energy effects and on collision-induced decompositions in organic mass spectrometry. He returned to Cambridge as a Sydney Harvey Research Fellow at Churchill College, and explored the applications of kinetic isotope effects to gas-phase ion chemistry. From 1972–1975 he held a Research Fellowship in The Research School of Chemistry at the Australian National University, Canberra, where his work included GC/MS analysis of insect secretions. Since 1975 he has been employed at the Shell Biosciences Laboratory, Sittingbourne, U.K., where his interests lie in the application of the full range of mass spectral techniques to the solution of agrochemical, biochemical, and environmental problems. In addition to research papers in the chemical literature, Dr. Howe has contributed review articles on two occasions to the Chemical Society publication "Specialist Periodical Reports" and has co-authored a book "Principles of Organic Mass Spectrometry" with D. H. Williams.

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confusing, and at times meaningless. The situation is now worse. Perhaps the most acute necessity for reform is found in the nomenclature adopted for new instrumental techniques, or combinations of old ones. Thus, while it is difficult enough for the layman to guess that PE/PI (*A3*), PIPECO (*H14*) and PEPICS (*N17*) are acronyms for the same technique, it is almost impossible to identify MS/MS, MI/CA (*Q39*) or simply MIKES (*Q35*) as all basically referring to the analysis by collision-induced dissociation of individual ions generated from mixtures. FI/CA (*K11*) and FI/CD (*I20*) have also been used to describe the above technique following field ionization, and Q/Q (*Q35*), ref 11) spectroscopy is likely to complicate the issue in the near future. Another problem in nomenclature is the loose definition of sensitivity. This is an unfortunate consequence of the drive toward lower detection limits. On a more general level, there are still several energy units in common usage, although this is not a problem for mass spectrometry alone.

However, remedial steps have been initiated. Under Beynon's chairmanship the IUPAC subcommission on mass spectrometry has put forward tentative recommendations on nomenclature for consideration by those practicing mass spectrometry (*A4*). It is hoped that authors and journals alike will comply with these recommendations.

SCOPE

Selection of material to be covered in this review is again unavoidable because of the increase in the number of activities which employ mass spectrometry, as indicated above. Thus, initially we cover advances in instrumentation and computer techniques, followed by a selective review of topics in gas-phase ion chemistry. We conclude with a range of applications, including natural product studies and biomedical and environmental advances. We have concentrated throughout on organic, as opposed to organometallic and inorganic chemistry. These omitted topics are well covered by Spalding (*B28*). There is also good coverage on a number of areas not mentioned in this review in the latest "Advances in Mass Spectrometry" volumes (*B8*). We believe that our literature survey has been almost exhaustive for North American, European, Russian, and Australasian journals although we have had to limit the number of references included in the review. The coverage extends from the previous cut-off point through December 1977 for American and British journals, and October or November 1977 for most others.

The *Mass Spectrometry Bulletin*, published from Aldermaston, England, since 1966 (*B20*) provides an exhaustive, but quite slow, coverage of the literature. The mass spectrometry bibliography prior to 1966 may be found in volumes by Waldron for 1938–57 (*B30*), by Elliott for 1958–60 (*B11*) and by Mead for 1961–62 (*B21*). Three international journals are devoted entirely to mass spectrometry: *Biomedical Mass Spectrometry* (*B5*), *International Journal of Mass Spectrometry and Ion Physics* (*B15*) and *Organic Mass Spectrometry* (*B24*). The last two appear monthly, the first bimonthly. Three compilations of mass spectral data are available: "Eight-peak Index of Mass Spectra" (*B10*), "Compilation of Mass Spectra Data" (*B7*) and "Registry of

Mass Spectral Data" (*B25*). Milne has reviewed the content of these publications (*B23*).

The Seventh International Conference on Mass Spectrometry was held in Florence, Italy, in August 1976 and the proceedings have eventually been published in two volumes (*B8*). The proceedings of the Annual Conferences on Mass Spectrometry and Allied Topics, the 24th of which was held in San Diego, Calif., and the 25th in Washington, D.C., are only produced for delegates and members of the American Society for Mass Spectrometry. The 1978 and 1979 meetings will take place in St. Louis, Mo., and Seattle, Wash., respectively. National mass spectrometry meetings are held annually in Britain, West Germany, and Japan. The Australia and New Zealand Society for Mass Spectrometry holds a biennial meeting. The international meetings on organic geochemistry are held biennially, the last being in Madrid in 1975 (*AG17*); the next will be held at Newcastle-on-Tyne, England. An International Symposium on Mass Spectrometry in Natural Products was held at Rehovot, Israel, in September 1977. A Symposium on Kinetic Mass Spectrometry and Analytical Applications was held in Moscow in October 1977. Two successful conferences were held on Topics in Ion Chemistry: the Euchem Conference on the Chemistry of Ion Beams (Nordwijk, The Netherlands, September 1977) and the 1st Sandbjerg Symposium on Organic Mass Spectrometry (Sandbjerg, Denmark, May 1977). The latter meeting was intended for the younger participants in ion chemistry research and as a consequence of the stimulating discussion that evolved, a 2nd Symposium will be held, at the same venue, in May 1978.

The Chemical Society publication, "Specialist Periodical Reports (Mass Spectrometry)", is now into volume 4 (*B18*) and once again has presented a high quality critical review of a wide range of topics and applications (covering mid-1974 through mid-1976). Edited by Johnstone, the volume includes chapters on theory and energetics (McMaster), structure and mechanisms (Bentley), computerized data acquisition and interpretation (Mellon), trends in instrumentation (McCormick), alternative methods of ionization and analysis (Wilson), field ionization and field desorption (Derrick), gas chromatography–mass spectrometry (Brooks and Middleditch), drug metabolism (Millard), negative ion chemical ionization (Jennings); reactions of organic functional groups: positive and negative ions (Bowie), natural products (Games), and organometallic compounds (Spalding). In most of the chapters, the authors have attempted much more than a cataloguing of references and their criticism is valuable. A cumulative index for Vol. 5 is promised and will be welcomed. A book by Millard on quantitative mass spectrometry has recently appeared (*B22*).

Lehman and Bursey have produced a book devoted to the theory and applications of the ICR technique (*M31*). Rosenstock et al. have produced an extensive compilation, "Energetics of Gaseous Ions" (*P13*), and happily another update is in preparation.

A large number of reviews have appeared on specific areas of mass spectrometry, including: charge localization in organic ions (*F29*), evaluation of potential energy surfaces (*Q53*), metastable ions and gaseous ion thermochemistry (*Q6*), onset potential determinations (*P12*), fundamental rate theories (*N16*), molecular orbital calculations for ionic species (*O30*), equilibrium constant measurements by ICR (*M18*), negative ions (*G3, G17*), field ionization and desorption (*C67, I35*), chemical ionization (*B26, J28*), collision induced decomposition (*K1, K13*) and its use in mixture analysis (*Q35*), collision-induced ion reactions (*B3*), and unimolecular chemistry of positive ions (*B31*).

Biomedicine. The increasing use of stable isotopes in biomedical research is reflected in the number of conferences held on the subject and the associated discipline of mass spectrometric quantification during the past two years. Within this context, a conference was held in Ghent in 1976 and the proceedings have been published as a book, "Quantitative Mass Spectrometry in Life Sciences" (*B9*). A second conference by the same organization will be held from June 13–16, 1978. This year will also have the Third International Conference on Stable Isotopes (Oak Brook, Ill., May 26–28) which again is largely devoted to mass spectrometric applications in biomedicine. Another stable isotope meeting was held in London in January 1977 and dealt with the use of labeled compounds in pharmacological, toxicological, and clinical research. Proceedings of this conference (edited by T. A. Baillie) will soon be published (*B2*). The annual "Mario-Negri" conferences were held in Milan in 1976 and Riva del Garda in 1977, and were entitled "Mass Spectrometry in Drug Metabolism" and "Mass Spectrometry in Biochemistry and Medicine", respectively. Proceedings of these conferences have been or are about to be published (*B12, B13*). "Advances in Mass Spectrometry", Vol. 7B, contains the proceedings of the biochemical applications presented at the International Mass Spectrometry Conference held in Florence in 1976 (*B8*).

Abramson has written a chapter on gas-phase analytical methods in a book entitled "Microtechniques for the Clinical Laboratory" in which he summarizes data on the impact of mass spectrometry and GC/MS in identification and measurement of biologically important compounds such as drug metabolites, steroids, and amino acids (*B1*). The use of GC/MS in laboratory medicine has also been discussed in a *Biomedical Mass Spectrometry* editorial by Odvar Stokke (*B29*). He stresses the problems of bridging the gap between the disciplines of mass spectrometry and biochemistry and medicine and stresses the importance of mass spectrometrists obtaining knowledge and interest in biochemistry if they are to provide useful service. Those interested specifically in the use of metabolic profiling by GC/MS should consult the excellent recent review by Jellum (*X17*) who has also published a review on the application of mass spectrometry to medical problems (*B17*).

Various chapters in "Mass Spectrometry, Vol. 4" are required reading for those interested in biochemical applications of mass spectrometry, particularly those entitled "Gas Chromatography-Mass Spectrometry", "Natural Products", and "Drug Metabolism" (*B18*).

Primarily aimed at those not too familiar with the technique of mass spectrometry is a short useful review by Jackson of its application in biochemical investigations (*B16*). He cites examples of the use of different ionization techniques (EI, CI, FD) in studies of the structures of porphyrins, alkaloids, taurine conjugates of bile acids, nucleotides, and antibiotics.

Kramer and McCloskey have recently reviewed the clinical uses of stable isotopes (*B19*). Rucher has published a review on the use of mass spectrometry in the quality control of drugs (*B27*) and in a similar vein, Brent and co-workers (*B6*) have written a chapter illustrating mass spectrometric applications in a pharmaceutical laboratory. They discuss SIM, mixture analysis by metastable ion methods and field desorption. Reviews by several authors have appeared on mass spectrometry in amino acid and peptide sequencing (*S2, S8, S26, S30*).

Considerable mass spectrometric data are also present in a book, "Antipsychotic Drugs, Pharmacodynamics and Pharmacokinetics", which was the proceedings of a conference held in Stockholm. The first three volumes (of nine) on "Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry" by B. J. and M. J. Gudzinowicz have been published (*B14*). The first volume deals in depth with respiratory gases, volatile anesthetics, and alcohol; the second is directed to hypnotics, anticonvulsants, and depressives; and the third, antipsychotics, antiemetic, and antidepressant drugs.

Derivatization is particularly important in mass spectrometric studies of biologically important molecules and a book has been published, edited by Blau and King (*B4*), in which different authors describe many of the most frequently used derivatization techniques, e.g., acylation, silylation, alkylation, cyclization, etc. Mass spectrometric data on certain compounds are also presented.

The reader will find that this review is by no means comprehensive, even for biomedical applications. One noticeable deficiency for example is discussion on respiratory gases and volatile anesthetics; those interested should consult a book previously mentioned (*B14*). Applications in plant biochemistry and insect metabolism and agriculture in general have not been discussed at all, even though mass spectrometry is widely used in all these disciplines, and only relatively little data on animal biochemistry have been discussed.

INNOVATIVE TECHNIQUES AND INSTRUMENTATION

Much of the innovation in mass spectrometry continues to

be triggered by the close association and collaboration of its physical and analytical specialists with their colleagues in the bio-organic, molecular biological, and environmental health fields. The physical and analytical specialists' intimate knowledge of the theory and techniques of ion production, ion optical configuration, ion detection, and computer technology can be brought to bear in new ways on the problems facing their bio-organic, molecular biological, and environmental health colleagues. Thus far, the two best forums for expression and cross-fertilization of instrumental potentiality and extant molecular analytical problems which are ripe for studies concerning elucidation of the nature and functioning of living systems are the meetings of the American Society for Mass Spectrometry and The International Triennial Mass Spectrometry Conferences (see section B). General reviews of instrumental advances and potentialities in this regard have been presented by McCormick (*C46*) and Franzen (*C22*).

Reviews addressed to currently practiced methods of ionization exist (*C19*) as well as detailed reviews on field ionization (*C18*) and field desorption (*C18*, *C67*). Schulten's review (*C67*) has covered most of the techniques and applications of field desorption, such as emitter preparation and sample handling as well as applications to carbohydrates, sulfates, nucelic acid derivatives, amino acids and peptides, steroids, porphyrins, carotenoids, lipids, biogenic amines, drugs and drug metabolites, biomacromolecules, inorganic salts, and metal chelates (184 references included).

Boerboom (*C9*) has indicated the application of quadrupoles, hexapoles, and, in general, multipoles in the analytical part of the mass spectrometer and compared them with the conventional magnetic sectors, and has provided an introduction to the application of microchannel plates and signal amplification. Present vacuum techniques from mass spectrometry applications have been discussed (*C30*). Prospects for enhanced performance of the mass filter have been presented (*C43*).

Gross has edited a volume entitled "High Performance Mass Spectrometry: Chemical Applications", which covers fundamental aspects of studies of gas-phase ions in terms of reaction mechanisms, their qualitative time dependence, FIK studies, enhancement of the internal energy by collision-induced dissociation, as well as a suite of analytical applications (*C28*). Hunt and Sethi (*C31*) have discussed selective ionization using both positively and negatively charged reagent gases as well as a pulsed positive ion, negative ion combination. Using the pulsed positive ion, negative ion (CI) technique the accuracy of mass measurement was preliminarily investigated (*C32*). Using a conventional mass spectrometer in the negative ion mode, qualitative analysis of lower mass alcohols, mercaptans, ketones, aldehydes, aliphatic carboxylic acids, and esters were characterized by intense $(M - H)^+$ ions (*C40*). Comparison with positive ion mass spectrometry was discussed.

Using phase-space dynamics in calculations of the performance of quadrupole devices, Dawson has illustrated the application to mass filter design studies and compares predicted results with experimental measurements (*C16*). Improvement in the transmission–resolution characteristics for quadrupole mass spectrometers has been shown using separated rf and dc fields in the entrance aperture (*C20*). Variations in the dispersion, resolution and inclination of the focal plane for a single focusing mass spectrometer have been carried out by the use of two quadrupoles (*C72*). Also, quadrupole lenses enable design of a "zoom mass spectrometer"—variable resolution— which can be investigated theoretically using a newly developed computer program TRIO (Third Order Ion Optics) (*C44*).

An ion optical system whose focal lines are vertical to the optical axis was studied mathematically and a prism mass spectrometer with two quadrupole lenses was chosen as a suitable system (*C69*). The use of crossed electric and magnetic fields has been employed to effect rapid electric scanning at constant accelerated voltage (*C56*). Characteristics of multipoint field ionization sources have been described and compared with activated tungsten wire emitters (*C12*).

Application of a new type field ionization source to mass spectrometry has been described and evaluated on a double focusing (*C2*) and quadrupole (*C1*) mass spectrometer. This volcano-type FI source yields excellent ion optical characteristics permitting good focusing in both the x and y directions. Also, since sample feed occurs through the central volcano hole, efficient ionization of the sample results. The design of a field ionization, field desorption electron impact ion source has been described and its performance evaluated on an A.E.I. MS-9 (*C58*). The use of a time-averaging computer as an integrator for peak matching high resolution FDMS using electrical detection has been described. Mass measurement accuracies better than 20 ppm have been obtained (*C59*). Computer-controlled data acquisition and on-line data processing, including multiscan averaging, have been described for field ionization kinetic experiments (*C74*).

The development of techniques which will permit generation of structural information on derivatized biopolymers is an important experimental technique thrust in present work. Several approaches are being pursued by various laboratories in parallel.

Curie-point pyrolysis techniques have been explored in combination with wall coated open tubular capillaries (*C17*), field ionization and field desorption mass spectrometry (*C66*), and products of high polymers (*C51*). Many related experimental techniques and applications may be found in the volume entitled "Analytical Pyrolysis" (*C3*).

Gaffney and Friedman have carried out rapid heating of fragile molecules using heated rhenium filament probes which can be heated at the rate of 15 000 K/s. CI and EI spectra were obtained in the parent region from dextrose, sucrose, and Na_2ATP (*C25*). A microcomputer-based temperature controller has been developed for direct inlet probe to a high resolution mass spectrometer (*C60*). A new design direct introduction probe tip for the CEC 21-110 mass spectrometer is described (*C19*).

In a number of areas of biochemical research, there is a growing need for high mass, high sensitivity mass spectrometry. This capability has been achieved recently using the Kratos/A.E.I. MS-50 by addition of a high field (23 kG) magnet so that scanning the range from 3000 atom mass units at full accelerating voltage 8 kV is possible with a resolving power up to $M/\Delta M$ 50 000.

Morris and co-workers (*C53*) have obtained an FD mass spectrum of sucrose octaoleate whose molecular weight is 2454 using this instrument and, in the more important application, have partially determined the structure of the antibiotic vancomycin, which until now has eluded identification by EI or FDMS techniques. The data obtained have demonstrated the molecular weight of the *N*-acetyl *O*-methyl derivative to be 1254 atomic mass units (*C54*). It is obvious that this technique will have a wide range of applications in the characterization of oligosaccharides, oligopeptides, and oligonucleotides, as well as mixed biopolymers. Phosphazines seem to be ideal compounds which will serve as high molecular weight internal mass markers for field desorption as well as electron impact mass spectrometry.

Olson et al. have assigned the compositions up to mass 2120 for one type of perfluorinated phosphazine (*I25*). Morris has shown that Peninsula Chemicals's Ultra-Mark 1621 can be used as mass calibration to mass 3150 (*C53*). Using photoplate high resolution mass spectrometry, studies of high molecular weight algal tanin derivatives have been presented to mass 2200 (*C33*). Once again the utility of a double beam mass spectrometer has been demonstrated for mass marking using field desorption and chemical ionization analyses (*C55*). More information is becoming available on the use of time-of-flight mass spectrometry of nonvolatile organic compounds by fast, heavy-ion-induced volatilization and ionization techniques (*C35*) [Californium-252 plasma desorption mass spectrometry (*C42*) and fission fragment-induced desorption (*C5*)].

Studies of thin films of Sm_2O_3 clusters and a Pt–thymine complex using 10-kV acceleration have extended the mass range of this technique to 4000. The minimum velocity necessary to effect secondary electron emission from an ion detector has been studied using gramicidin-A whose molecular weight is 1881 (*C8*, *C63*).

The ionization of molecules by alkali ion attachment on the surface of a field anode covered with salts has been previously demonstrated with polar molecules and recently the fragmentation of $[M + Li]^+$ ions has been studied by collision-induced dissocation techniques (*C63*). It is also of interest that the $[M + Li]^+$ ion of neopentane had been observed (*C10*). A primary argon ion beam of extremely low current density

has been used to obtain spectra of amino acids from a nearly undisturbed surface (*C6*). Spectra of amino acids obtained in this way are in good agreement with those obtained by the californium-252 technique (*C42*) reported by MacFarlane and Torgeson. Laser microprobe mass spectrometric techniques have been investigated for obtaining mass spectral information on some organic polymers (*C73*).

Since the major portions of ejected particles produced by noble gas ion bombardment of surfaces are neutral atoms or molecules, a method for determination of the mass spectra of sputtered neutrals has been described and some aspects of this technique for surface analysis and depth profiling of anoxide layers of Nb and Ta are discussed (*C57*).

Experiments attempting to apply electron, proton, and hydride ion transfer reactions in a tandem mass spectrometer for the analysis of large organic molecules and the characterization of complex, multicomponent mixtures have shown that the choice of reagent ions is limited only by the availability of an ion beam with sufficient intensity for these highly specific chemical ionization experiments (*C68*).

With the recent proliferation of interest in experimental arrangements which produce both positive and negative ions with low internal energy ("soft" ionization techniques), the development of collision-induced enhancement of ion internal energy is becoming a very important area of study, both in the invention of new techniques as well as in their ever-increasing use in different fundamental and analytical applications. Not only do molecular ions and quasi-molecular ions with sufficiently low internal energy require collision-induced dissociation in order to obtain structural information by generation of an ensuing fragmentation pattern, but elucidation of the composition of ion clusters formed from reagent gases and solvated ions can be aided by the enhancement of the molecular clusters' internal energy sufficient to dissociate the clusters (solvation ligands) without breaking the primary bonds of the molecular ions' original carbon skeleton. This has been shown to be a potential solution to ion clustering interferences in API mass spectrometry (*C23*).

Time-of-flight mass spectrometers (*C26*), reverse geometry double focusing mass spectrometers (*C76*), and field ionization mass spectrometers (*C49*) have been modified for the observation of collision-induced dissociation spectra. Using such techniques, volatilization of mixtures, their ionization, ion separation, and subsequent nominal mass specific collision-induced dissociation have been used as an alternative to a chromatographic separation followed by ionization and mass analysis (*C34*, *C36*). Of course, initial ion separation can be carried out at higher mass resolution raised to essentially any separation ($M/\Delta M$) degree desired. Elemental compositional specificity of the ionic series may thus be obtained before their subjection to collision-induced dissociation and recording of their metastable ion fragmentation patterns (*C47*, *C48*).

Specific detection of particular trace components in gasoline such as thiophene, tetrahydropyran, and propylbenzene have been carried out at the 50-ppm level (*C48*). Similar studies on isomeric $C_5H_{10}O$ ketone mixtures have been reported (*C37*). The sequence of amino acids in simple oligopeptides and their mixtures has been obtained in analogous fashion (*C65*).

Using double-focusing mass spectrometers, various types of linked scans of accelerating and electric sector voltages have been described and utilized in conjunction with the observation of collision-induced dissocation fragmentation patterns (*C11*, *C50*, *C77*). A particular linked B/E scan has been developed for the observation of metastable transitions at high resolution occurring between the ion source and the electric sector—the first field-free region. Placement of a collision cell near the ion source in this region leads to high sensitivity collision-induced high resolution metastable ion spectra since the ion source accelerating voltage is held constant and the ion production and extraction characteristics remain unchanged (*C13*, *C62*). A collision grid instead of a collision cell has been described also in this connection (*C62*). The appearance of peaks at non-integral masses in linked scans of the type where the ratio of B/E is held constant has been shown to be caused by fragmentation of metastable ions occurring in the field-free region between magnetic and electric sectors (*C52*).

A method for the deconvolution of composite metastable peaks occurring in the first field-free region of a reverse geometry mass spectrometer has been described (*C21*). Three-dimensional representation of metastable peaks from double focusing mass spectrometers yields a surface which provides a unified view of various alternative methods of scanning and facilitates an understanding of the contrasting perspectives of the metastable peaks which the surfaces reveal (*C39*).

Computerized methods for automatically acquiring metastable ion data in a double focusing mass spectrometer with reverse geometry have been described (*C4*). Also computers have been used to assist in the interpretation of the shapes of metastable peaks (*C29*).

Metastable ions generated by chemical ionization have been compared with those generated by electron impact (*C14*) and a simple technique of shape determination of metastable peaks at constant source conditions has been used for the measurement of kinetic energy release (*C38*).

A velocity threshold of $\sim 5 \times 10^6$ cm/s has been observed as the limiting factor in the use of secondary electron detection for the observation of high molecular weight ions (*C8*, *C63*). A ±200 000-V post-acceleration detector for positive and negative "macro" ions has been discussed (*C8*). Pulse counting and single ion counting techniques in low and high resolution mass spectrometry have been described (*C24*, *C61*, *C75*). Discussion of the effective dead time of pulse counting detection systems has been presented (*C27*) and variance analysis of error in selected ion monitoring assays using various internal standards has been published (*C15*). The relative contributions of sample manipulation and GC/MS analysis to the total observed error for the analysis of imipramine and desipramine in serum using $^2H_4$-labeled internal standards has been determined by this variance analysis technique.

A display device for ion beam profiles has been described which will permit the study of a mass spectrometer's ion source performance (*C64*). Development of a simultaneous ion detector consisting of a channeltron electron multiplier array with phosphor screen and videcon multichannel analyzer combination has been described (*C72*) and a similar device utilized with a variable mass dispersion laser pyrolysis and collision-induced dissociation studies (*C71*).

A system has been described in which the effluent of a gas chromatograph is directly combusted and transmitted to a mass spectrometer for measurement of the isotope ratio of CO_2, H_2O, N_2, etc. (*C45*). Calculation of the isotopic composition of synthetically labeled substances has been carried out when the label is deuterium and the molecule has an M–H peak (*C7*). A computer program for determining the degree of labeling for any stable isotope has been described (*C67a*). Using ultra-high resolution mass spectrometric analysis ($M/\Delta M > 100\,000$) for the separation of $^{12}C^2H$ vs. $^{13}C^1H$ type mass clusters and computer isobaric modeling techniques, multiple stable isotope incorporation for more than one isotopic isobar has been carried out for bile acids isolated from in-vivo studies of the rat during administration of various carbon-13 and deuterium-labeled ethanols (*C78*).

CHROMATOGRAPHIC–MASS SPECTROMETRIC–ON-LINE COMPUTER TECHNIQUES

Detailed reviews by C. J. W. Brooks and three sequential chronological updates by Brooks and Middleditch have documented the salient advances in methodology and extensive applications of GC/MS—the most recent of these covering literature through June 1976 comprising 674 references to the original literature (*D8*). No other such complete treatments of the extensive and growing applications of GC/MS exist and, hence, their consultation from biomedical through pharmacological, microbiological, toxicological, environmental, and inorganic applications is mandatory (Volume 5 in this series will include a cumulative index when it appears). The most significant recent advances in this technique have occurred due to the *combined* utilization of the developments of splitless sample injection (*D24*, *D25*), the preparation (*D26*), and evaluation (*D4*, *D23*) of the operation and sustained performance of wall coated open tubular (WCOT) columns, and open split (*A3*) and/or direct connection of the GC capillary to the ion sources of mass spectrometers. Cram and Risby (*D12*) have treated GC and GC/MS in this issue and their review should be consulted for detailed information on the present GC capabilities themselves.

The optimization of the parameters controlling ion source sensitivity, mass spectral scan cycle time, and chromatographic elution profile as well as on-line computer systems to record, display in real-time, and subsequently evaluate these sets of GC/MS data is also mandatory for full utilization of present GC/MS potentialities. While the foregoing applies chiefly to electron impact ionization, analogous developments for chemical ionization (*D7, D34*) and field ionization (*D19, D20*) are of course complementary and in some cases of primary significance (*D7*).

High Resolution Gas Chromatography/High and Low Resolution Mass Spectrometry. Several factors have limited the rate at which glass open tubular capillary columns have been adopted in GC/MS analysis of biologically interesting mixtures (particularly in the United States). These include: lack of commercial availability, difficult methods of preparation, problems in direct coupling to mass spectrometers, too slow mass spectrum scanning speed, and low sensitivity on some instruments. Development of computer methods for improving the apparent resolution of packed gas chromatographic columns (maximizing ion techniques) has also dissuaded some workers from adopting capillary columns.

However, many of these reasons no longer apply and capillary columns are increasingly being used in all branches of analytical biochemistry. Several commercial firms market glass wall coated open tubular (WCOT) columns and methods for consistent production of columns of adequate resolution have been published by the Grob family (*D26*). Even high resolution mass spectrometers have been directly interfaced with high resolution capillary columns, thereby giving rise to an exceedingly powerful technique (*D11, D32*). This latter development has particular importance in analytical problems where sample scarcity allows only few or single GC/MS runs and maximum information (high resolution mass spectra and elemental composition chromatograms) should be obtained.

This increasing use of capillary columns need not conflict with the method of improving apparent column resolution by data processing techniques. Use of these techniques will also improve capillary column resolution and, more important, will allow much greater sensitivity by lowering background and producing sharper peaks. Clearly, however, the maximum utilization of the resolving power of capillary columns is very dependent on the instrument's ability to scan rapidly while maintaining sufficient ion statistics per mass peak. Development of multichannel array detectors will solve this present situation (see below).

An interesting development in multicomponent capillary column GC/MS analysis has been published by Blum and Richter (*D7*). They have demonstrated the usefulness of parallel FID and TIC recording in GC/CIMS where the reagent gas is frequently changed. Since the gas chromatograms obtained by flame ionization detection are unaffected by changes in chemical ionization conditions, they provide a safer common basis for interrelating spectral data from successive runs than do the TIC records. The potential of this method was realized when it was found that the use of more than one CI reagent could result in new, complementary structural evidence and thus provide a means of selective probing of certain structural features.

Specific suggestions as to solvent-free and splitless injection methods for open tubular columns have been made (*D14*). Dual column operation for GC/MS has been described (*D31*). Heart cutting techniques for high resolution gas chromatography applied to cigarette smoke have been used (*D6*) and a freezer-separator suggested for the concentration of carrier gas containing separated mixtures prior to introduction of the sample into the suitable detector (*D21*). The lack of carrier effect in GC/MS for selected ion monitoring using isotopically labeled internal standards has been expressed (*D39*).

Calculation of retention indices of compounds from their structural formulas for identification by GC/MS has been presented for aliphatic alcohols and saturated hydrocarbons (*D43*). Discussion of the modes of interfacing gas chromatography systems with mass spectrometers has been described in our previous review (*A3*). The disadvantages of various noble metal and stainless steel restrictor capillaries in terms of selective absorption have been shown by Grob (*D22*) and Axelson (*D4*); hence, for use of open tubular capillary columns, open splits, or direct connections with glass restrictor capillaries properly treated for deactivation of absorptive sites are preferred in order to preserve chromatographic performance and qualitative component fidelity. Capillary GC/MS-computer techniques have been described for the quantitation of *N*-nitrosodimethylamine in air collected on Tenax. Also, ambient levels of halogenated organics were determined (*D10*).

Mellon (*D38*) has reviewed the computerized data acquisition and interpretation advances for mass spectrometry through June 1976. Vigorous development activity is still going on aimed at perfecting and tailoring software of various laboratories' "home grown" computer systems for more effective and facile treatment and interpretation of GC/MS data in particular. Commercial data systems have attempted to include many of the refinements developed in various expert laboratories, but the stand-alone commercial packages are still plagued with software bugs and inadequacies.

A system on a PDP 11/45 has been described for the study of components in drug metabolism from GC/MS runs (*D44*). Sjövall and co-workers (*D1*) have demonstrated one outstanding use of computerized GC/MS for the analysis of metabolic profiles of bile acids in urine using a lipophilic anion exchanger where over 30 individual bile acids were completely or partially identified from urine of healthy subjects and patients with hepatobiliary diseases.

Further efforts aimed at extraction of mass spectra free of background and neighboring component contributions from packed column GC/MS data (*D15*) have permitted the quantitative comparison of entire historical GC/MS profiles of complex mixtures with those of new mixtures using constantly updated historical libraries of previously recorded GC/MS profiles and "clean" mass spectra from related mixtures. The organic acid fractions of human urine were used as an example of the performance of this system (*D42*). A similar approach also using packed GC columns coated with OV-17 has been developed independently by Sweeley and co-workers (*D45*). This approach is designed to utilize characteristic ions in each component's mass spectrum combined with a retention index window for location, identification, and quantitation of each component in a GC/MS run of urinary organic acids. This software system, called MSSMET, presently reports the relative, semiquantiative amounts of some 50 to 100 components in each such GC/MS run for inter-GC/MS-metabolic-profile comparison. Work on determination of relative sensitivities of each component would of course permit quantitation in milligrams per milliliter of urine. Presently, relative concentrations of particular components may be compared from GC/MS run to GC/MS run without the need for measuring the components' mass spectral sensitivity factor.

Liquid Chromatography/Mass Spectrometry (LC/MS). Another potentially advantageous area is the effort being devoted toward development of combinations of liquid chromatographic systems with mass spectrometers; however, the levels of utilization from the point of view of the types of molecules which are most amenable to HPLC separation vs. interface and mass spectral characterization are still so significantly disparate that these developments must be considered exploratory from an analytical point of view.

One commercially available LC/MS interface which will permit the continuous introduction of effluent from the liquid chromatograph into the mass spectrometer is the moving endless thin ribbon (*D36*). This system has been used to evaluate the liquefied coal products as new materials for fuel or petrochemical feed stocks. HPLC separation of these products by the number of condensed rings yields fractions which were further separated and evaluted by LC/MS. A Waters LC has been interfaced to a commercial GC/MS data system for the separation and identification of drugs and drug related compounds (*D28, D29*).

Another LC/CI quadrupole combined instrument has been described and used for studies of polychlorinated benzenes and pesticide mixtures (*D2*). Considerations of the nature of capillary flow of volatile liquids from atmospheric pressure to vacuum have been described in connection with analytical mass spectrometers (*D46*) and a freezer-separator suggested for the concentration of carrier gas containing separated mixtures prior to introduction of the sample into the suitable detector (*D21*).

An instrument applying laser vaporization and molecular beam techniques to achieve rapid heating while minimizing

contact of a nonvolatile sample (solute) with solid surfaces has been described. Spectra of pyrimidines and purines as well as arginine, glycine, and histidine were obtained. Spectra obtained were comparable to electron impact probe samples (*D35*).

Selected Ion Monitoring. This has become a very widely used technique in all branches of analytical chemistry in the life sciences and a historical account of it has recently been published by Falkner (*D16*). It is defined as dedication of a mass spectrometer to the acquisition of ion abundance data at only selected masses in real time as components emerge from the chromatographic system. The nomenclature surrounding this and allied techniques is still being hotly debated and for full descriptions and criticism of the abbreviations currently in use, the reader should consult the reviews of Falkner et al. (*D17*) and Budde and Eichelberger (*D9*). Falkner and co-workers (*D17*) strongly suggest the term *selected ion monitoring* (SIM) for the act and *selected ion current profile* (SICP) for the output. Consistent with the definition of SIM, a SICP is then a plot of the change in ion abundance as a function of time, using abundances measured by SIM. Budde and Eichelberger (*D9*) strongly recommend that these terms be adopted and we agree that they are appropriate.

Precise terminology is particularly important because there are several other widely used techniques that may be confused with SIM and SICP, one of which is the form of data output following continuous repetititve measurement of spectra (CRMS). These terminology problems have been discussed by Budde and Eichelberger (*D9*) who recommend the use of the following acronyms: TICP (total ion current profile) defined as a normalized plot of the sum of the ion abundance measurements in each member of a series of mass spectra as a function of the serially indexed spectrum number (TICP) will depend on the mass range chosen for CRMS and should not be confused with the output from continuous monitoring of the unresolved ion beam. This plot should be similar to the TICP but contains contributions from ions outside the "window" imposed during CRMS. The classical "TIC" record should perhaps be known as the unresolved ion profile (UIP), formed as a result of unresolved ion monitoring (UIM).

The data reduction technique which is most often confused with SICP is plots of change of relative abundance of one or several ions as a function of time from CRMS data. Hites and Biemann suggested the name mass chromatogram but Budde and Eichelberger have proposed extracted ion current profile (EICP) because the data for the few ions used in the plot are extracted from the larger set used to generate a TICP.

One of the disadvantages of SIM is the limited number of compounds that can be assayed per GC run since most available instrumentation only allows measurement of up to eight ions. Sweeley et al. (*D20a*, *X28*) have described a technique called *multiple ion set-selected ion monitoring* (MIS-SIM) by which the number of compounds that can be assayed in a single run is increased dramatically. In magnetic sector instruments, this has been achieved by alteration of the magnetic field settings several times during the course of a single GC analysis. Since the maximum time required to establish a new setting of the magnet is about 8 s, peaks as close as 1 min apart can be quantitated with ease. These workers have expanded the technique by identifying components by use of retention indices held in a small reference library in the computer. Quantitation by SIM and by CRMS have been compared by Sweeley et al. for a series of organic acids. They found that, compared to CRMS, SIM had higher precision, higher sensitivity, and greater linear range but the number of compounds which could be determined simultaneously was lower.

MASS SPECTRAL INTERPRETATION AND MANAGEMENT TECHNIQUES

Certainly the single most helpful, most cost-effective component of any mass spectrometry laboratory is its own dedicated computer system, be it "home-grown" or of commercial origin. It should not be the limiting factor in either the quality of the mass spectral data obtainable from the laboratory's instruments or the primary data processing and presentation of mass spectral information during which this initial quality is preserved. It should permit the interactive interrogation and assessment of its disk and tape files as well as provide facilities for hard copy of user-judged important information. Specialized (laboratory tailored) library storage and retrieval facility is necessary. The major questions outstanding are the nature and accessibility of the more specialized and sophisticated low and high resolution mass spectral interpretive programs as well as the remote access to one or more centralized, general mass spectral library systems by some form of computer networking. All forms of "computer-aided identification" of mass spectra depend to a *primary* extent on the existence and quality of a mass spectrum of the unrecognized substance in question in the library in question, or something whose fragmentation pattern or characteristics are sufficiently closely related that it is useful to have knowledge of if retrieved. A point which seems to this reviewer sufficiently important that at this stage in the development of computerized interpretive mass spectrometry it cannot be overemphasized, is that high accuracy mass measurements yielding elemental composition assignments for the compound in question are as foolproof a way of ascertaining the nature of an important unknown as any of the techniques presently under vigorous development (*E5*, *E11*) based on combinations of library search and structure–spectra correlations. When elemental compositional determinations are available, the heuristic programs coupled with computer methods for exhaustive, nonredundant structure and substructure generation will yield the maximum advantage for ultimate identification.

Emphasis at this stage of development of mass spectrometry should focus clearly on comprehensive mass spectrometry analytical systems whose individual functional component quality is carefully designed and performance understood. In the case of GC/MS, as pointed out in section C above, the quality of the injector, the absorptive properties and acidity or basicity of the chromatographic column, the details of the interface to the ion source (be it electron bombardment, chemical ionization, or field ionization), the ion optics of the instrument, the mass spectral pattern stability and reproducibility, the signal-to-noise of the detector system, the dynamic range and quality of the algorithms, the on-line computer reduction and processing capability, the clean-up of mass spectra eliminating column bleed, background, and the attempted resolution of unresolved chromatographic components are all of very high importance to system overall perormance.

Tremendous emphasis has been placed and is continuing to be expended on the generation, maintenance, and availability of small, dedicated as well as comprehensive libraries and search and retrieval methods for access directly and remotely by networks to these libraries.

A concomitant problem of course involves the interpretation of mass spectra—particularly unknowns—or groups of known spectra of related substances from existing libraries or particular research projects. Pesyna and McLafferty brought the literature together on computerized structure retrieval and interpretation of mass spectra including a discussion of inductive and deductive approaches and their combinations [187 references through the mid-70's (*E33*)]. Mellon (*D38*) and others (*E3*, *E23*) have reviewed this area in the same time frame. Dromey has described a library search scheme which retains class definition of the file using a simple ion series related index and which still yields close to an order of magnitude reduction in the search space (*E19*). Computer methods have been described for automatic identification of compound classes in GC/MS analysis by combination of mass chromatograms (*E12*) and automatic classification of computer extracted mass spectra (*E22*, *AG84*). A program has been described which automatically compares a file of spectra number-cleaned-up mass spectrum pairs from a GC/MS analysis with a library of retention index-mass spectrum pairs (*E6*). Further work on reverse search methods has been reported (*E18*, *E24*, *E34*). Discussions of encoding techniques which are a quick filtering process using functional group assignment and structural correlation have been presented (*E30*) as well as discussions of the reduction of file searching costs by selective searching of an ordered library (*E20*). A comparative study of methods of computer matching of mass spectra based on one laboratory's utilization bias has chosen the "big six" and "big eight" peaks methods (*E27*). The Abrahamsson computer file has been described which contains

40 000 mass spectra (*E2*). The process of the MSDC/NIH/EPA mass spectral search system has been presented (*E21*). The NIH/EPA chemical information system has been described (*E31*). The aim of the latter is to produce a series of searchable chemical data bases usable by working analytical chemists with no special computer expertise and also to link data bases together so the user need not be restricted to a consideration of, for example, only mass spectral data. Description modular libraries of mass spectra and digital cartridges have appeared (*E4*). A program for the interpretation of the mass spectra of π metallic complexes claims their structure may be determined in a few seconds using this approach (*E25*). Further work on computerized pattern recognition discusses the survey of correlations between pharmacological activities and mass spectra (*E1*). Work on the factor analysis for mass spectra has continued (*E35*, *E36*, *E42*). Using the same data base and the same 20 substructures, a computer pattern recognition technique has been compared with McLafferty's STIRS system (*E26*). McLafferty has recently brought attention to the need for reliable ways to evaluate performance, prediction, and evaluation in the identification of mass spectra using different computerized retrieval and interpretation systems. Criteria are recommended for comparing and improving such systems and for evaluating the reliability of a system's predictions for a particular unknown spectrum (*E28*). McLafferty's group has continued the vigorous development of a retrieval probability-based matching (PBM) system and an interpretive self-training interpretive and retrieval system (STIRS). For general introductions to this approach, one is referred to Pesnya and McLafferty (*E33*). More recent discussions of STIRS development (*E43*, *E44*) and detailed discussions of information from characteristic ions (*E14*), information on substructural probabilities (*E17*), increased information from neutral loss data (*E16*), prediction of rings-plus-double-bonds-values (*E15*), and an algorithm which compares two molecules to identify the largest common substructures (*E13*) have been documented. Varkony, Carhart, and Smith have continued to develop and articulate heuristic artificial intelligence methods for the computer-assisted elucidation of structure based to a large extent upon low and high resolution mass spectral data (*E41*). The general problem is of course complex since analytic relationships between mass spectral fragmentation processes and molecular structure and stereochemical features do not presently exist. Hence the use of computer techniques for the exhaustive, nonredundant generation of structure is of paramount importance for comparison with other chemical and mass spectral information obtainable. Interactive computer programs have been used to study the questions concerning plausible ion structures (*E39*). Since mathematically analytic relationships do not exist [such as is the case in chemical shift correlations with molecular structure in carbon-13 nuclear magnetic resonance spectroscopy (*E7a*)], empirical rules are generated from a knowledge of heuristic correlations of mass spectra and molecular structure. Computer programs can be used to help discover such rules from empirical data on known compounds. One program called Meta-DENDRAL uses heuristic methods to search for common structural environments around those bonds that are found to fragment and abstracts plausible fragmentation rules (*E7*). Further programs such as CONGEN are able to construct possible solutions to structural elucidation problems from atoms in other structural units supplied by the chemist. Methods of implementation of constraints on the program CONGEN have been discussed in terms of adopting an emulation of a chemist's reasoning about molecular structures (*E9*). CONGEN has been utilized to investigate two aspects of the structural isomerism of mono- and sesquiterpenoid skeletons. The first being the scope of possible isomers under various structural constraints and the second, the scope of possible isomers based on a mechanistic model which allows interactive exploration of reactions of formation and interconversion. Warning is presented of potential danger in structural assignment based on currently known biosynthetic grounds (*E39*). Using similar and other programs, computer-assigned structural elucidation considering the ranking of candidate structures based on comparison between predicted and observed mass spectra has been presented (*E40*). The Stanford group had discussed a number of approaches to extend the concept of computer-assisted structure elucidation beyond simple structure generation and have discussed how chemical information together with a computer program can assist chemists in both planning prior to structure generation and subsequently in the testing of candidate structures (*E10*). These concepts and programs also have yielded an approach which is capable of emulating many of the laboratory applications of sequences of chemical reactions for their application to both mechanistic and structural problems. Sasaki and co-workers have described an attempt to feed several types of physical data acquired by computers from mass spectrometers, NMR, IR, and UV spectrometers into a central computer program to effect structural elucidation based on a combination of all four types of data (*E37*).

Finally, consideration of the exportability of remote usage of these sophisticated, specialized computer aids to structure elucidation is at issue. Discussions of computer networking and an associated collaborative research community have been presented using a case study based on the DENDRAL programs (*E8*). In addition, the computer identification and interpretation of unknown mass spectra utilizing a computer network system has been discussed (*E45*). Two international computer networking systems, MSDC/CYPHERNET and Cornell/TYMNET are available to permit outside users access to McLafferty's STIRS system (*E29*). The SUMEX-AIM (Stanford University's Medical Experimental Computer-Artificial Intelligence in Medicine) system is internationally available over TYMNET (*E8*). The questions of intersystem quality, demonstration of their performance for backup for aiding the stand-alone laboratory in mass spectrometry's analytical problems and, last but not least, the cost to outside users have yet to be clearly established.

TOPICS IN GAS-PHASE ION CHEMISTRY

The sections included below are intended to encompass the topics concerned with the various fundamental processes occurring in the mass spectrometer. This broad field of interest continues to expand and the coverage here incorporates: unimolecular decomposition following EI ionization, alternative ionization methods (negative-ionization, PI, FI, FD), ion/molecule reactions (CI, CID, HPMS, ICR), various theoretical treatments (energetic and kinetic), and energy measured in ionic decompositions. A brief rationale of isomerization reactions is included. Inevitably there are areas of overlap but hopefully these have been minimized by cross-reference.

Electron-Impact (EI) Ionization and Decomposition. Despite the various alternative ionization techniques now available, electron-impact ionization remains by far the most common technique employed in organic mass spectrometry. New classes of synthetic compounds and natural products continue to be classified by their mass spectral reactions after electron impact; and many compounds are re-examined (often by isotopic labeling and at different internal energies) to evaluate fully the decomposition processes involved. Because of the large number of publications which utilize electron impact techniques, this section of the review is highly selective and covers just a few of the more important points not reported in the specialist sections below.

Williams and Beynon have carefully reviewed the evidence for and against the concept of charge and radical localization in organic ions (*F29*). It was concluded that, despite some weaknesses, the model serves a useful function in explaining and predicting the unimolecular fragmentation pathways which occur. The concept should be rejected only when an alternative and more useful hypothesis becomes available (*F29*). The site of ionization is often a point of conjecture and clues about this have been obtained from the ionization potentials of bifunctional compounds (*F1*, *F2*, *F29*).

Ortho effects in mass spectrometry continue to supply instances of unusual reactions which, although difficult to explain in detail, are diagnostically useful for structural identification (*F5*, *F7*, *F17*, *F20*, *F22*, *F23*, *F27*). For example, neighboring-group participation was invoked to explain some unusual C–O bond cleavages in ester (*F23*) and ether (*F7*) groups. However, ortho effects constitute only one type of functional group interaction. There are many instances of decompositions in mass spectrometry which result from remote interactions, usually involving either cyclizations (e.g., *F4*, *F16*, *F26*) or hydrogen transfers via cyclic transition states

(e.g., *F6, F18, F28*). It was shown that alkane elimination from ketones is sometimes a lower energy reaction than the McLafferty rearrangement (*F18*); but in the mass spectra of allenes the McLafferty rearrangement is a significant process (*F28*).

Differences in stereochemistry are frequently not detectable by mass spectrometry, either because of loss of configuration in the molecular ion or because the difference in reactivity between the stereoisomeric ions is small. However, there are many known exceptions and these have been reviewed by Green (*F13*). Cyclic alcohols and diols are frequently reported examples in the literature (*F11, F15, F19, F24, F25, F30*). The most striking example occurs in a series of 3- and 4-arylcyclohexanols where there are large differences in the extent of H_2O loss between some of the cis and trans isomers (*F24*). Stereochemical effects continue to be observed in the mass spectra of steroids; the rate of the retro-Diels-Alder reaction from a series of Δ^7-steroidal olefins shows a marked dependence on the stereochemistry of the A/B ring junction in accord with orbital symmetry rules for a thermal concerted process (*F10*). The temperature dependence of a stereoselective reaction has been investigated and surprisingly appears to follow the kinetics of the Arrhenius equation (*F14*). Kinetic deuterium isotope effects continue to be reported (*F3, F9, F12, F28*), in mass spectral reactions, although they are sometimes difficult to quantify when hydrogen "scrambling" interferes with measurements (see section on isomerization reactions below).

The vast majority of electron-impact studies to date have concentrated on the ionic products of mass spectral reactions, but it is possible to collect and analyze the neutral species expelled (*F8, F21*). An apparatus has been devised to investigate the structures of neutral C_4H_8 isomers eliminated from *n*-butylphenylether (*F8*). "Neutral fragment" mass spectra and ionization potentials of neutrals have been measured for a series of substituted benzenes by use of a dual-ionization source (*F21*).

Negative Ions. Mass spectrometry of negative ions is now used increasingly in the solution of structural and analytical problems (for reviews, see *G3, G14, G17*). This is because the technique has been developed to yield structural information with adequate sensitivity for an increasing number of compound classes. Impressive results in negative-ion chemical ionization mass spectrometry are responsible for much of this upsurge of interest and are covered in the section on chemical ionization (CI) below.

Negative ion production in the gas phase basically occurs by one of three mechanisms: (1) electron attachment (capture), (2) dissociative electron capture, or (3) ion-pair production. Mechanisms 1 and 2 require the generation of a sufficient population of near thermal electrons and this condition may be satisfied at high sample pressures (*G23, G24*), under CI conditions (*G19, G25*) and by modification of ion source potentials (*G26*). Compounds of certain structural types (having high electron affinities) are more amenable than others for generation of suitable negative ion spectra, but instrumental parameters are equally critical (*G26*). Primary electrons of 70 eV are usually employed in negative ion studies and sample pressure necessary for sufficient negative ion current production ranges between 10^{-7} Torr (*G26*) and 10^{-4} Torr (*G23*). Many of the negative-ion studies in the recent literature have been carried out on compounds of high electron affinities, e.g., β-diketonate copper complexes (*G16*), fluorinated β-diketones (*G18*), oximes (*G9, G11*), thioesters (*G27*), nitrophenyl-TMS ethers (*G7*), and natural products with "tags" for electron capture (*G15, G29, U3, U19, U40*). The general problem is that many molecular anions are short-lived and unstable, e.g., benzene and alkylbenzene anions eject electrons back into the continuum within 10^{-14} s (*G20*, see also *G21*). However, molecular weight and structural information are obtainable from certain compounds.

Bowie et al. have continued to explore the diversities of negative-ion organic mass spectrometry. Doubly-charged negative ions have been generated in the analyzer region of a double-focusing mass spectrometer by the process $A^- + e \rightarrow A^{2-}$ (*G7, G12*) and have been detected in an ICR cell (*G28*). The dissociative spectra of positive ions (including flavones) produced by collision-induced charge inversion from negative ions have been observed (*G1, G4, G5*). Metastable reactions of negative ions have been investigated (both unimolecular and collision-induced) (*G10, G13*) and associated measurements of kinetic energy release have been used in structural and mechanistic studies of anion behavior (*G6, G8, G22*). Deuterium isotope effects have been observed for hydrogen transfer reactions during unimolecular anion decompositions (*G2, G30*). It is interesting that the magnitude of k_H/k_D is little different in the source compared with metastable reactions. This is because molecular anions are considered to have uniformly low energy (*G2*).

Photoionization (PI). The application of photoelectron-photoion coincidence (PEPICS) spectroscopy to kinetic studies in mass spectrometry is becoming widespread (*H6, H13, H14, H21–H24, N1*). This technique permits the evaluation of unimolecular rate constants and translational energy releases at selected internal energies (particularly in the metastable-ion energy range). Therefore it provides a means for testing fundamental rate theories (see relevant section below). Reactions of ions formed in different electronic and vibrational states are conveniently studied by the PEPICS technique (e.g., methyl halide cations, *H6, H14* and NO^+, *H23*). The principle and experimental procedure have been well reviewed by McMaster (*H13*). Positive ions are formed by photoionization (e.g., from a hydrogen- or helium-line source) and are accelerated by a constant applied field (typically ~ 5 V cm^{-1}) in the opposite direction to the photoelectrons produced. The ions are mass-analyzed and the photoelectrons are energy-analyzed and detected in delayed coincidence with the corresponding ions. By this means, a time-of-flight spectrum of a given ion is obtained for a given parent-ion internal energy. Electron-energy resolution as low as 30 meV has been reported (*H14*).

Photoionization is the most precise method for determining ionization potentials (IP) and appearance potentials (AP) (see *P12* and section on Appearance Potentials below). An accuracy ± 1 meV was reported for the IP of H_2 (*H18*), but for polyatomic ions the error is somewhat higher. For example, the IP's of dimethyl and diethyl ether have been determined to a precision of 10 meV. Differences in the IP's compared with previous results are attributable to "hot band" effects (*H1*). PI-efficiency curves for molecular and fragment ions from these ethers yield information on AP's, heats of formation and fragmentation mechanisms with accuracy and detail not possible by other methods. Similarly PI studies on benzene and its diyne isomers have revealed new information about breakdown mechanisms of the molecular ions. Autoionization takes place in the benzene cation and decomposition occurs via two pairs of noncompeting reactions (*H20*). IP's and AP's have been measured from PI-efficiency curves for fragmentations of H_2CO, HDCO, and D_2CO (*H12*), in which unusually large isotope effects were observed.

The thermochemistry of some fluorinated propanes (*H27*) and fluoromethylsilanes (*H15*) has also been determined by PI methods. By appropriate use of thermochemical cycles, the proton affinities of CH_2CHF and CH_2CF_2 were calculated, independently of the heats of formation of any neutrals (*H27*, see also *H26*). Interesting threshold–PI results have been reported on toluene and cycloheptatriene (*H25*): $C_7H_7^+$ formed from both sources appears to be the tropylium ion.

Dunbar et al. have continued their investigations of the photodissociation spectroscopy (PDS) of organic cations trapped in an ICR cell. Analysis of kinetic data from the PDS of brombenzene cations has confirmed that dissociation occurs via a sequential two-photon mechanism (*H3*). Beauchamp et al. have demonstrated similar two-photon dissociations in benzene (*H8*) and benzonitrile (*H17*). PDS facilitates the assignments of states for organic cations and measurements on the methyl–naphthalene system appear to be particularly secure (*H5*). Assignments for halotoluene cations and their isomeric benzyl halides are interesting: it is apparent from time-resolved PDS that the benzyl halide cations have partially rearranged to an isomeric structure (*H10*). Among other ions studied by PDS are $C_4H_8^+$ (*H19*), $C_6H_5CO^+$ (*H9*), $C_6H_6COCH_2CH_2CH_3^+$ (*H11*), and protonated hexamethylbenzene (*H4*). It is suggested that the photodissociation of the butyrophenone cation via the McLafferty rearrangement proceeds through isolated electronic states (*H11*).

PDS will typically yield an optical resolution of 10–20 nm and the higher resolution (~ 1 nm) required to reveal vibrational fine structure is now attainable via laser-induced photodissociation (*H2, H5, H7*). The *trans*-1,3,5-hexatriene

cation displays vibrational fine structure (*H2*) in its laser-PDS in contrast to the toluene cation which does not exhibit the expected fine structure (*H7*).

Photon irradiation has also been applied in conjunction with field ionization. When the emitter tip (tungsten) is illuminated by an external light source, enhanced ionization occurs for photon energies of lower value than the work function of tungsten (*H16*).

Field Ionization (FI) and Field Desorption (FD). Field ionization occurs when a compound is subjected to a high electric-field gradient such as that created at either a sharp tip or thin wire anode. The method is termed field desorption when the compound is coated on the tip or wire. Despite the criticisms of insensitivity and nonreproducibility, the use of FI and FD is still on the increase. Trends in instrumentation and applications have been reviewed by Schulten (*I35*) and Derrick (*I9*) and theoretical explanations of the ionization mechanisms have been described (*I13, I16, I17*).

The most important consideration in any FI/FD experiment is the quality of the emitter and problems which have arisen in emitter preparation include (a) lengthy procedure, (b) complicated preparation methods, and (c) unreliable emitter quality. This has resulted in an interest in new methods of emitter preparation. Instead of wires or blades, the use of etched tungsten foils as emitters in FI has been described (*I1*). Foils, however, are not suitable for FI kinetics studies, because of uneveness at the edges (*I1*). Relatively inexpensive electrochemical methods of emitter preparation have been described (*I7, I29*). Other considerations in the choice of emitter type are the thermal stability of the compound to be desorbed and the appearance potentials of ion products (*I30*). Instead of activated emitters, untreated 10-μm tungsten wires have been used as anodes for FD of salts (*I30*), sugars (*I12, I31*), peptides and nucleotides (*I43*). The potential of untreated wire emitters has been described, including the ionization of nonelectrolytes by the addition of acids or salts (*I12*). Metal dendrites have been employed for aromatization during field ionization (*I10*). An important factor influencing FD spectra reproducibility is emitter temperature (*I45*) and the development of emission-controlled emitter heating has helped to alleviate this problem (*I21, I36, I46*).

Two significant publications have shown that heated FD emitters may be used simply as direct insertion probes in electron impact and chemical ionization sources without application of a high electric field. In the EI mode ionization by the electron beam occurs after thermal desorption from the wire (*I37*). Spectra of sodium salts are obtainable by this method. In the CI mode, methane CI spectra were similarly obtained of salts and thermally labile organics at the 100-ng to 1-μg level (*I15*). For both of the above techniques, some source modification is required.

The formation and decomposition of doubly-charged ions observed in FI spectra have been investigated (*I8, I23, I32*). It is believed that M^{2+} ions are formed via a second ionization process of the adsorbed M^+ ions on the anode surface (*I23*) and the temperature and pressure dependence of M^{2+} abundance from the field ionization of diphenyl ether supports this mechanism (*I23*). In the FI spectra of alkylbenzenes doubly charged fragment-ion-radicals appear to be formed via a different adsorption state of the singly charged species than in the case of M^{2+} formation (*I32*).

Field desorption now enjoys widespread use in natural product studies and in certain industrial chemical analyses. Among compound classes studied have been: oligosaccharides (*I28, U28, U29*), peptides (*I26, S9, S18, S56*), nucleosides (*T8*), nucleotides (*T16*), carotenoids (*I44*), biogenic amines (*I48*), sulfonic acids (*I22*), ionic dyes (*I19*), quarternary ammonium salts (*I42*), and ketopiperazines (*I38*). Addition of metallic ions is sometimes an advantage, either to promote desorption or to assist counting of spectra. In the Li^+ attachment to D-glucose at high electric fields, virtually the only ion in the spectrum is $M + Li^+$ (*I11*).

The main advantage of FI/FD as an analytical tool lies in the molecular weight information obtainable. The technique is therefore suitable on occasions for mixture analysis (*I18, I20, I34*). The lack of breakdown ions leads to difficulties in mass counting, especially in the absence of a data system, and phosphazenes are among compounds suggested as high mass references (*I25*). Impressive high-mass FD spectra (>mass 2000) have been reported for sucrose polyesters (*I33*).

Field ionization kinetics (FIK) continues to be used to determine the mechanisms of ion decompositions occurring in periods as low as picoseconds. Standardization of the methods of normalizing rates of decomposition in FIK has been a problem and Beckey, Levsen, and Derrick have suggested a definition of the "normalized rate" (*I3*, see also *I2* for related constructive evidence). Data processing of FIK data is time-consuming and computer programs have been written to reduce the data (*I27, I40*). Van der Greef and Nibbering have successfully applied the high voltage scanning technique to the detection of fragmentations of gaseous ions generated by FD, in the time range 10 ps to 1 ns. The method, which incorporates an automatic emitter–temperature regulator, is termed FD kinetics (*I39*).

One advantage of the FIK method is that at the lower end (1 ps) of the time range of study, molecular ions may be assumed to have the same structure as the unionized molecule and it is in the range 1 ps to 1 ns that many of the faster rearrangements in organic ions occur. For example, it has been shown by FIK that specific hydrogen interchanges occur within 1 ns in the molecular ion of 3-phenylpropanal (*I47*) and C–C equilibrations take place in the molecular ion of 2-phenoxyethylchloride (*I41*). It was even possible to distinguish by FIK between a nonspecific hydrogen rearrangement and hydrogen scrambling, since the kinetics of both processes differ considerably (*I4*). The FIK technique has proved particularly useful in investigating isomerization reactions in aliphatic hydrocarbon ions: in the isomeric C_8H_{16} molecular cations, ring opening occurs within 1 ns if 3-, 4-, or 5-membered rings are present (*I5, I6*). FIK studies in the picosecond range have identified methylcyclopropane-type intermediates in skeletal rearrangements of the $C_4H_8^+$ system (*I24*, see also *I14*).

Chemical Ionization (CI). When a molecular sample is ionized in a high-pressure ion source via an ion–molecule reaction with an ionized reagent gas, the sample is said to undergo chemical ionization. CI is now employed widely in chemical analysis and structural elucidation (for reviews, see *J28, J39*). Molecular weight information is obtainable from sample quantities comparable to those employed in EI ionization and the signal enhancement (compared with EI) in the molecular-ion region is frequently dramatic (*J13, J28, J29, J39, J40*). The choice of reagent gas remains critical, but largely empirical. The conventional CI gases, methane and isobutane, are being superseded for selected positive-ion applications by ammonia (*J2, J29, J37, J38*), water (*J26, J38*), hydrogen (*J2, J24, J34*) and combinations of these with inert gases (*J23*, see also *J28, J39*). Furthermore a novel method has been employed in which salt hydrates are used to generate water in situ on the probe (*J4*). In another interesting development Hunt et al. have obtained CI spectra of salts and thermally labile organic compounds by using FD emitters as solid probes (*I15*).

For the full evaluation of the potential of CI it is necessary to discover more about the ionization process, molecular-ion structure and breakdown mechanism with various reagent gases. CI spectra of isomers often supply useful information about ion structures. For example, benzyl halides and halotoluenes have similar EI mass spectra but their CI spectra (H_2 and CH_4) are quite different, illustrating that the respective $M + H^+$ ions are structurally distinct (*J24*). The ionization modes of the two main ions in the methane plasma in reaction with *n*-paraffins have been studied (*J20*). $C_2H_5^+$ acts as a hydride-acceptor (with subsequent hydrogen randomization in the $M^+ - H$ ion) and CH_5^+ as a proton–donor (forming a short-lived protonated alkane ion which does not rearrange). In the methane CI spectra of a series of cyclohexyl derivatives $C_6D_{11}X$, intramolecular hydrogen rearrangements increase in extent with increasing proton affinity of the derivative (*J21*, see *J3, J8, J25, S5* for other discussions of hydrogen rearrangements in $M + H^+$ ions). The relative abundance of $M + H^+$ ion occasionally has structural significance (*J23, J36*). In a series of polycyclic aromatic hydrocarbons the $(M + 1)^+/M^+$ intensity ratio from an Ar/CH_4 ionizing medium is reproducibly structure-dependent (*J23*). The site of protonation on a series of substituted benzenes has been investigated by D_2O-CI. Aniline, benzaldehyde, and nitrobenzene protonate on the substituent and bromobenzene, iodobenzene, and biphenyl on the ring (*J26*). Long-range interactions in some protonated bifunctional molecules have been noted (*J14, J37*) and the reactions observed supersede

those which are characteristic of the individual functions (*J37*).

CI spectra of natural products are now widely reported (*J11, S7, S10, S20, S52, U7, U17, U25, U37, U38*). Molecular-weight and structural information is obtainable and the choice of reagent gas is important. For example, the H_2–CI spectra of amino acids provide more structural information than the CH_4 spectra (*J34*, see also *J19, J27, O4, S10, S20, S36, S52* for other amino acid CI spectra). NH_3–CI had been used in the natural product field (*J29, S10, U7*), especially in carbohydrate identification. An example of its application is found in the CI analysis of triglycerides (*J29*): no $M + H^+$ ions are observed with isobutane, but with ammonia the $M + NH_4^+$ ion is the base peak.

The importance of CI in GC/MS studies is being generally recognized (*J17*), with and without a separator. A detection technique has been described in which a selected reactant ion in the CI plasma is continuously monitored (*J18*). By use of a low-energy reactant, this method may be made compound-class selective (*J18*).

It has been recognized that CIMS may reveal stereochemical effects which are not evident in EI fragmentations. ^{18}O labeling has shown that a series of isomeric hydroxymethyl α-decalols exhibit a striking difference between the reactivity of the primary and secondary hydroxyls (*J30*). Acetylation in the CI source of diacetoxynorbornane isomers occurs to greatly differing extents and steric arguments accommodate the results (*J16*). Other CI spectral differences between isomers have been emphasized (*J5, J10, J12, J32, J35, J36*), notably between diterpene isomers (*J31*). Selection rules for pericyclic processes have been applied to the CI spectra of some isomeric cyclopropylmethyl ethers (*J1, J2*). The extent of CH_3OH elimination is consistent with theoretical predictions and parallels solvolysis rates of analogous tosylates in solution (*J2*). An interesting effect has been observed in the CI spectra of enantiomeric dimethyl tartrates (*J9*). Chirality is preserved (at least partly) in the 2M + 1 cations: deuterium labeling shows that D–D and L–L association is considerably stronger than D–L interaction in 2M + 1 ion formation (*J9*).

It has become evident recently that negative-ion CI is as sensitive as positive-ion CI and in certain cases up to two orders of magnitude more sensitive. Hunt et al. have described the analytical applications of several negative-ion CI reagent gases in enhancing the sample ion-current (*G19*) and Jennings has reviewed the topic (*J22*). Frequently a *mixture* of gases provides the best conditions for anion formation from the parent molecule and a few percent of added gas can totally change the reagent anions present in the plasma. Among reagent anions that have been employed are: CH_3O^-, $CH_3COCH_2^-$, $CH_2NO_2^-$, $CH_2NO_2^-$, CCl_3^-, C_2H^-, O^-, O_2^-, OH^-, and Cl^- (*G19, J22*). In certain cases, detection and identification below the picogram level are possible (*G19*) and where a direct sensitivity comparison with positive-ion CI has been made, the negative mode provides the greater ion current (*G19, G25*).

The reactions of O^- (derived from NO_2, CO_2 or N_2O) with organic species have been studied in a CI source (*J6, J15*, see also *J7*). Among the characteristic reactions undergone by this radical anion in H_2^+ abstraction to form H_2O. This reaction is prominent with 1-alkenes (*J6*) and with activated CH_2 groups (*e.g., those adjacent to carbonyl groups, J15*). The negative-ion CI of OH^- has also been investigated (*J33*). The OH^- ion is formed with high intensity by electron bombardment of N_2O/H_2 and N_2O/CH_4 mixtures at total pressures of 1–3 Torr. In many cases, H^+ abstraction from the sample is the characteristic ionizing reaction (*J33*).

Collision-Induced Dissociation. When an ion of high translational energy (>1 keV) collides with a neutral molecule and undergoes excitation (usually electronic), any subsequent decomposition is known as collision-induced dissociation. The collisional-activation (CA) spectrum of an ion is defined as the mass vs. abundance data from this dissociation (for reviews, see *K1, K13*). CA has become commonplace and commercial instruments now incorporate collision cells for operation in the field-free regions, usually at pressures between 10^{-4} and 10^{-5} Torr. The CA experiment in most cases consists of activating nondecomposing ions which have a lifetime of about 1 μs. Subsequent decomposition occurs and the CA spectra are often similar to those obtained by EI. Advantages of CA are (1) the technique can be applied to fragment ions and (2) the spectrum obtained is largely independent of the internal energy of the incipient ion. The mechanism of energy transfer has been discussed at length and it appears that the energy added by collision is distributed randomly in the ion, according to the tenets of the QET. McLafferty and Wachs, pioneers in the field, have confirmed this property for methane decomposition (*K22*). The efficiency of CA has also been investigated (*K8*).

The reactions and structures of long-lived $C_8H_9^+$ isomers have been extensively investigated by CA (*K9, K10*). Distinction between 13 isomers was possible, partly with the assistance of deuterium labeling. The study indicated that one can identify structural entities in molecules by measurement of fragment ion CA spectra (*K10*). Other hydrocarbon cation isomers examined by CA include $C_3H_7^+$ (*K4*), $C_4H_8^+$ (*K16*), $C_5H_{10}^+$ and $C_6H_{12}^+$ (*K17*). Some of the isomeric hexenes showed differences in CA spectra useful for structural characterization (*K17*). The various butyl cations which have long been known to isomerize to common structures below the threshold for decomposition can be partly distinguished by gas-phase derivatization (*K5*). Condensation products formed by reaction with furan or acetic acid in the ion source are investigated subsequently in a collision cell (*K5*). When heteroatoms are present, the identification by CA of structurally distinct isomeric ions is often possible, e.g., $C_6H_6O^+$ (*K2*), $C_2H_3N^+$ (*K21*), $C_8H_{14}O^+$ (*K19*), $C_5H_8O^+$ and $C_7H_{12}O^+$ (*K6*). The frequently-studied phenol cation was differentiated from its cyclohexadienone isomer by CA measurements (*K2*). The mechanisms of some neighboring-group interactions have also been investigated by CA (*K12, K20*).

McLafferty et al. have described an instrumental modification (a separate ion chamber) which enables separation of the "unimolecular" element from CA spectra (*K23*). The technique shows that a relatively small proportion of ions in CA spectra arise from purely unimolecular processes (*K23*). Other types of reaction occur in the collision cell apart from electronic excitation to a monocharged species and products of the charge-stripping reaction, $A^+ + N \rightarrow A^{2+} + N + e$, have been identified (*K7*). For a number of monosubstituted benzenes, there appears to be little advantage of this method over EI for structural elucidation (*K7*). However, charge-stripping CA has been used to distinguish between $C_5H_6^+$ isomers where singly-charged CA fails (*K15*). The collisional activation of $M + Li^+$ ions formed by Li attachment yields fragment ions which retain the Li atom and are structurally informative (*K18*). The CA spectra of negative organic ions have also been obtained (*G10*) but a collision gas may invert the charge and induce decomposition (*K3*). A quantitative analytical application of CA has been described in which 50-nmol samples of underivatized amino acids may be field-ionized and quantitatively analyzed for ^{15}N content (*K14*). CA also appears to offer considerable promise in mixture analysis (*I20, K11, Q35, Q39*, see also section on metastable ions below).

High-Pressure Mass Spectrometry (HPMS). This technique covers experiments in gas-phase ion molecule chemistry in a high-pressure ion-source. The special case of chemical ionization (CI) mass spectrometry was covered in a preceding section of this review.

Despite the development of ICR spectrometry for measurement of accurate equilibrium constants in the gas-phase, HPMS (at ion-source pressures as high as several Torr) remains a reliable method for achieving the same results. As with ICR, conditions must be arranged so that true equilibrium has been attained at the time of ion concentration measurements. Kebarle et al. have measured the intrinsic gas-phase acidities of a series of 50 benzoic acids and phenols from gas-phase proton transfer equilibria at 600 K (*L7*). A pulsed-electron beam was used which resulted in equilibrium attainment after 100 μs. The substituent effects on gas-phase acidities for both benzoic acids and phenols largely followed the same order as in solutions. In the benzoic acid series an interesting exception was the *p*-OH substituent, which carries a more acidic proton than the carboxyl group. The gas-phase acidities of a collection of carbon and nitrogen acids yield several disparities with solution data which illustrate the importance of solvation energies in determining solution acidities (*L6*). The same group have determined a number of proton affinities (*L5, L18*) and gas-phase basicities (*L18*) by pulsed positive-ion HPMS and have used their high-

pressure source to investigate carbonylation (*L4*) and hydration (*L3, L4*) of carbocations. The kinetics and equilibria involving the penta-coordinated carbonium ions $C_2H_7^+$, $C_3H_9^+$, and $C_4H_{11}^+$ were investigated between −160 and 200 °C (*L2*). Isomers of these species were identified.

Field et al. have investigated by HPMS the reversible hydride ion transfers between various alkyl (*L9, L10*) and cyclic hydrocarbon (*L16*) ions. From variation of equilibrium constants over a wide temperature range, hydride ion affinities were calculated which indicated that the norbornyl cation is ~42 kJmol^{-1} more stable than would be expected for a secondary species (*L16*). Other hydrocarbon ion/molecule reactions studied by HPMS have involved ethylene (*L15*) and aromatic hydrocarbons (*L14*). It was found that stablized benzene dimers are produced via a third-order process in which isotopic scrambling does not ocur between benzene moieties (*L14*). Ion molecule reactions involving fluorinated hydrocarbons have been reported (*L12, L17*), as with ICR. Proton transfer reactions have been studied between cyclic borazine cations (*L1*) and between magnesium atoms and various proton donors at high temperatures (*L13*).

Proton-bound dimers frequently occur in the high-pressure mass spectra of amines and other proton acceptors. Braumann et al. have analyzed the rate of $2M^+ + H$ formation from NH_3, CH_3NH_2, and $(CH_3)_2NH$ in terms of the RRKM theory as applied to an intermediate collision complex (*L11*). The temperature and pressure dependence of $2M^+ + 1$ formation were accurately predicted (*L11*). The observation of cluster ions is becoming more common and H_2O and H_2S were shown by HPMS to form various clusters by association with themselves and each other (*L8*).

Ion Cyclotron Resonance (ICR). Ion/molecule reactions in the gas-phase can be most easily studied by either ICR or high-pressure mass spectrometry and, judging from the volume of publications in the recent literature, ICR has become the method of choice in the majority of cases. Several recent reviews of aspects of ICR spectrometry are recommended. Lehman and Bursey have produced a useful book devoted to the theory and applications of the ICR technique (*M31*); Wilson has reviewed the ICR literature for the two years up to June 1976 (*M52*); and Bowers et al. have discussed at length the measurement of, and problems associated with, gas-phase ion/molecule equilibrium constants in the ICR cell (*M18*). Fourier-transform ICR has been discussed (*M15*) and non-computer methods for improving mass measurement accuracy have been presented (*M30*). Instrumental innovations include an ICR cell capable of operating in the temperature range 80–450 K (*M10*) and a pulsed-ICR cell for investigating emission spectra produced in thermal ion/molecule reactions (*M37*).

Many of the ICR papers in the recent literature have been concerned with the determination of acid/base properties of ions in the gas-phase free from solvent interactions. The research groups of Beauchamp and Bowers have been particularly active in this field. To effect such determinations, it is necessary to establish an acid base ion/molecule equilibrium in the ICR cell. This condition is usually achieved either by trapping ions for periods as long as several seconds, or by operating at sufficiently high pressures. Enthalpy changes and other thermodynamical quantities are then calculated (to a best accuracy of 0.8 kJ mol^{-1}) from equilibrium constants. However, it has been emphasized that contributions to entropy changes due to intermolecular interactions between ions and molecules should be ignored (*M33*). Comparison of acid–base properties in the gas-phase with those found in solution has led to a redefinition of the relative importance of inductive effects, polarizability, and solvation energy in solution.

Proton affinities (PA) of series of alkyl, alicyclic, and saturated heterocyclic amines have been measured by ICR (*M3*). The changes in PA were interpreted in terms of a charge-induced dipole model (*M3*). In a related study, a detailed explanation of differences between gas-phase and solution basicities of alkylamines was given and the importance of electrostatic solvation in solution was emphasized (*M4*, see also *M5*). The decreasing effect of fluoroalkyl substitution on the gas-phase PA of amines was interpreted in terms of a direct inductive effect (*M45*). A pulsed ICR method for precise evaluation of proton transfer equilibrium constants has been applied to a wide range of C, N, O, P, S, As, and Se bases, and the results provide insights into the intrinsic effects of molecular structure on base strength (*M55*). The PA's of phenol (*M20*) dihalocarbenes (*M32*), and nitriles (*M44*) and the base strength of fluoroethanes (*M46*) have been measured. ICR methods have also been used to determine the site of protonation on aniline in the gas-phase, which is the NH_2 group (*M40*). However in certain substituted anlines, ring protonation was inferred and the role of solvent in this process in solution was discussed (*M47*, see also *M2, M9, M16, M21, M29, M35, M48* for other site-of-protonation studies). Site-selectivity has also been shown to occur during hydride-ion abstraction from alkanes in the gas-phase (*M34*). There has ben some discussion as to whether gas-phase ionic equilibria have been reached in the ICR experiment (*M18*) but from pressure-variation and trapped-ion studies the proton transfer to aliphatic alcohols and amines has been shown to occur at the ion–molecule encounter rate (*M36*). The possibility of photoexcitation of ions in the gas-phase has revealed a new field of research in which gas-phase, acid–base properties are evaluated for excited states of ions. Changes in acidity and basicity are employed to suggest changes in electron distributions and dipole moments for excited states, and to discover the types of transitions involved (*M25, M26*).

The equilibrium constants for gas-phase proton transfers between negative ions have also been reproducibly measured by ICR spectrometry. The acidity of alkanethiols increases with increasing alkyl size in the gas-phase but the opposite effect is found in solution (*M8*). The entropy of ionization is considered to be the main factor causing the reversed acidity order. Other ICR studies on negative ions have yielded acidities of fluoroalcohols (*M19*) silanes (*M39*), and trimethylborane (*M38*). The kinetics of proton transfer between a number of delocalized anions have been investigated by pulsed ICR. These reactions, although exothermic, are often quite slow (*M24*).

Many of the ICR research papers reported in the literature, however, are concerned merely with the types of gas-phase, ion/molecule reactions occurring and not necessarily with thermodynamical quantities. Differences between isomers are sometimes discerned by ICR measurements where unimolecular ion-chemistry cannot differentiate. For example, the benzene cation is distinct from isomeric hexadiynes in its reaction with $(CH_3)_2CHI$ (*M27*). Stereochemical effects have been observed in the ion/molecule reactions of some norbornyl isomers (*M28*). ICR has shown that the $C_6H_5^+$ ion is a strong electrophile, attacking σ- and π-electron systems (*M43*) and both electrophilic (*M14*) and nucleophilic (*M12*) gas-phase aromatic substitutions have been reported. ICR measurements on deuterium-labeled acetanilides and phenyl acetates have confirmed that the parent cations eliminate ketene via 4-membered transition states, yielding, respectively, the aniline and phenol cations (*M50*). Among other compounds investigated by ICR methods are: aliphatic ketones (*M51*), propionitrile (*M49*), fluorinated hydrocarbons (*M22, M42*), and vinyl methyl ether (*M23*). Reactions of organometallic ions have been studied (*M1, M6, M7, M17*) as well as an anionic polymerization (*M11*) and benzoylation reactions in the gas-phase (*M13*). Equilibrium isotope effects have been measured (*M53, M54*) and it has been shown how bimolecular rate constants for protonation of some cyclic hydrocarbons can be employed to detect common intermediates (*M41*).

Fundamental Rate Theories. In recent years, there has been an upsurge of interest in the theories of unimolecular reaction kinetics, particularly as applied to polyatomic ions. Qualitative interpretations of mass spectral features in terms of the Quasi-Equilibrium Theory (QET) of mass spectra have been supplied on numerous occasions over the past decade; but quantitative predictions have largely been confined to small ions. The current status of the QET has been well reviewed by Lifshitz (*N16*).

The technique of photoelectron–photoion coincidence spectroscopy (PEPICS) has recently become available for calculating the unimolecular rate constant $k(E)$ for fragmentation as a function of internal energy. Furthermore, experimental determination of kinetic energy distributions in products of unimolecular ionic reactions is now possible by the PEPICS technique and both these procedures provide a means for testing rate theories (*H14, H21–H24, N17*). Statistical phase space theory has been applied along with the QET to the elimination of HCN from the benzonitrile mo-

lecular ion (*N5*). Upper limits for $k(E)$ were obtained from the phase space theory calculations, as a consequence of the transition state being "product-like" (*N5*, see also *N14*). The QET gave a better fit with experiment for $k(E)$ but the kinetic energy distribution of products was much more adequately explained by the phase space theory (*N5*). The QET is useful for predicting properties near the transition state and not in the product region of the potential surface. Other comparisons between phase space theory and the QET in terms of kinetic energy product distributions have been made and defects discussed (*N2*, *N15*). Phase space theory predicts accurately the product kinetic energy distribution in the ion/molecule reaction $C_2H_4 + C_2H_4^+ \rightarrow C_3H_5^+ + CH_3$ (*N4*, *N15*), but for other ion/molecule reactions the agreement was poor (*N3*). In all unimolecular rate theory calculations, the choice and nature of the transition state are of the utmost importance and have been discussed at length (*N7–N9*, *N11–N13*).

The unimolecular fragmentation of the benzene molecule-ion and some of its diyne isomers have been studied in the 5–500 μs range. The decay curves implicate multiple reactive states and are therefore not at variance with the tenets of the QET (*N6*). Similarly, decay rates for loss of X from metastable energy-selected $C_6H_5X^+$ ions are in excellent agreement with the QET, in contrast with calculations on $C_4H_6^+$ reaction rates (*N1*). Breakdown curves for deuterated propanes agree generally, but not exactly, with those calculated by the QET. Hydrogen randomization is a problem in this instance (*N20*). Some metastable decompositions of deuterated methanes have been explained in terms of quantum mechanical tunnelling (*N18*, see also *N19*). From kinetic isotope effects on some hydrogen transfer reactions, comments were made on early transition state demands (*N10*).

Molecular-Orbital (MO) Calculations. Despite the large amount of mass spectrometric data accumulated on the energies of polyatomic ions, relatively little is known about the corresponding structures. However, the improvement in reliability of MO methods in relating an ion structure to its energy is contributing to a change in the above situation; and the structures of ions and their breakdown mechanisms in the mass spectrometer are being identified with greater certainty.

MO studies on polyatomic ions have been reviewed by Pople (*O30*) and McMaster (*O27*). Ab initio MO methods (*O21*), which incorporate no simplifying approximations in the evaluation of energy integrals, are regarded as a more satisfactory base for theories of structure than semi-empirical methods such as CNDO, INDO and MINDO (*O30*). However, it is contended that at the cheapest level of ab initio calculations, using the lowest minimal basis set, the results are not predictive and the MINDO/3 method gives more reliable predictions (*O27*). More expensive ab initio calculations using larger basis sets are necessary to achieve useful predictive results (*O27*).

Further studies have been reported on the long-standing problem of the $C_7H_7^+$ structure. Dewar et al. describe MINDO/3 calculations of the potential surface for the benzyl → tropylium cation conversion (*O6*). The mechanism suggested is via the norcaradienyl and 1-cycloheptatrienyl cations with an overall activation energy of 135 kJ mol^{-1}. The corresponding ab initio calculations have been extended to predict the potential surfaces for the rearrangement of substituted benzyl cations to the corresponding tropylium ions (O*11*). It is suggested that *p*-hydroxybenzyl is more stable than hydroxytropylium and the barrier to rearrangement is high. However MINDO/3 appears to overestimate the stability of the substituted tropylium ions. The same authors have used MINDO/3 to calculate heats of formation, molecular geometries and charge distributions for monosubstituted tropylium and benzyl cations (*O12*). The interconversion between the toluene and cycloheptatriene molecular ions has also been investigated by MINDO/3 (*O10*). An interesting feature was the prediction of the hydrogen "scrambling" processes, which agreed with previous results. Another MINDO/3 calculation estimated the relative stabilities of the 2-norbornyl cation isomers (*O9*, see also *O5*, *O19*). The potential energy surface for loss of H_2 from the allyl cation $C_3H_5^+$ was estimated using MINDO/3 and found to predict correctly the translational energy released (*Q36*). Elimination of H_2 has also been investigated by this MO method from $C_2H_6^+$, $C_2H_5^+$, CH_2OH^+, CH_2SH^+ and CH_5N^+ (*O13*).

Ab initio MO calculations have been performed on the following ions: the phenyl cation, $C_6H_5^+$, the singlet state is found to be 84 kJ mol^{-1} below the lower triplet (*O14*); $C_3H_3^+$, the cyclopropenium ion is the most stable isomer (*O31*); $C_2H_3^+$, the classical (linear) and nonclassical (bridged) structures have similar energies (*O36*); $C_4H_5^+$, the methylcyclopropenyl cation, has the lowest energy (*O22*); $C_5H_9^+$ (*O29*); substituted vinyl cations (*O2*); protonated carbonyl molecules, R_2COH^+ (*O8*); oxygen- and sulfur-containing carbanions (*O17*, *O25*); and multiply-charged monocyclic aromatic cations (*O32*).

Calculations which are increasingly subjected to verification (e.g., by ICR) are of proton affinities and basicities in the gas phase (*O7*, *O8*, *O15*, *O24*, *O34*). INDO-type calculations on the structure of the protonated glycine ion have given credence to the stability of this ion in CI spectra (*O4*). IP's and AP's have also been estimated by MO methods (*O3*, *O16*, *O18*, *O20*, *O23*, *O26*, *O33*, *O35*, *O37*). Applications of state correlation diagrams to mass spectral decompositions are few, although the decomposition of the acetaldehyde parent ion is explainable by this means (*O28*).

Appearance Potentials. This section is concerned with methods used for the evaluation of appearance potentials (AP), ionization potentials (IP), and heats of formation (ΔH_f) of gaseous organic ions. Reference to related aspects of ion thermochemistry is found in the sections on MO Calculations (above) and Metastable Ions (below).

It has become increasingly necessary in mass spectrometry to determine AP's and IP's to a high accuracy, in order to evaluate precise ionic ΔH_f values. Such determinations are required in the elucidation of ion structures, potential surfaces, and reaction mechanisms and to test the reliability of MO calculations. It is also important to evaluate and anticipate any systematic discrepancies (e.g., kinetic shift) in AP and IP measurements.

In a highly recommended and comprehensive review, Rosenstock has summarized and critically discussed the 19 distinct measurement techniques used for AP and IP determinations (*P12*). Special attention was paid to the accuracies and limitations of the techniques available. In addition to this review, the recent compilation of "Energetics of Gaseous Ions" by Rosenstock, Draxl, Steiner, and Herron is recommended as an asset for anyone who regularly requires energetic data in mass spectrometry (*P13*). Some of the data, however, have been superseded by better values since compilation.

Photoionization remains the most precise method for determining IP's and AP's (see section on Photoionization above). Measurements have been reproducible to ±1 meV in certain cases (*H18*), but more often to ±10 meV (*H1*).

Lossing et al. have continued their accurate IP and AP measurements using an energy-resolved electron beam (of width ~70 meV) from a double-hemispherical energy selector, coupled to a quadrupole ion-filter (*P2*, *P6*, *P7*, *P19*, *Q28*). Repeated measurements of the ionization efficiency curves were taken and the data reduced by minicomputer to yield quoted accuracies of better than 50 meV. The substantial cataloguing of the IP's of hydrocarbon radicals has continued with measurements by these authors on C_5–C_7 alkyl radicals (*P6*, *P7*). The AP's measured by the same workers for RCO_2H_2 formation from RCO_2R^1 are consistent with H transfer to two separate oxygen atoms (*P2*). Other examples of the use of AP measurements in ion-structure and fragmentation-mechanism determination have been published (e.g., *F19*, *P8*, *P9*, *P11*, *P14*, *P16*, *P17*).

A number of methods have been developed for calculating or estimating IP's, AP's activation energies and ΔH_f values of gaseous positive ions and are largely covered in other sections of this review (see particularly the sections on MO Calculations and Metastable Ions). In the past, correlations with various Hammett Sigma constants have been used to estimate the IP's of substituted and disubstituted benzenes and efforts to use σ_p^+ values for this purpose have been critically discussed (*P1*). Such methods are not yet completely reliable. Linear free energy relationships between the IP's of aliphatic compounds have been investigated (*P4*): the influence of X on the IP of CH_3X is explainable in terms of hyperconjugation, rather than induction. A number of theoretical methods have been employed for calculating IP's via Koopman's theorem. These methods have met with limited success (*P10*, *P15*, *P20*).

A procedure has been devised for estimating ΔH_f for gaseous

cations from core electron binding energies (*P5*). ΔH_f values accurate to ±42 kJ mol^{-1} were estimated for 156 polyatomic ions containing a variety of elements (*P5*). It is frequently desirable in the evaluation of potential surfaces to estimate the ΔH_f values of gaseous cations and Bowen and Williams have reported a method applicable to open-chain cations (*P3*). The same authors have illustrated (by reference to some monosubstituted benzenes) that an upper and lower limit can be placed on the ΔH_f of a gaseous daughter ion, by appropriate consideration of reactions occurring, or not occurring, from the parent ion (*P18*).

Translational Energy Release: Metastable Ions. For the present purpose, metastable ions are defined as those which decompose in the flight path of a mass spectrometer at some point between the source and collector. Most of these low energy ions have lifetimes of the order of microseconds. Various techniques are available for studying metastable decompositions and it is a routine operation on many commerical instruments to determine not only the masses of precursor and product ions but also the translational (kinetic) energy (T) released in the reaction. Determination of T yields useful information on ion structures and decomposition mechanisms and T values as low as 1 meV can be evaluated. The book by Cooks, Beynon, Caprioli, and Lester (*Q11*) still remains an informative text on metastable ions, despite recent advances; and reviews that are highly recommended are by Williams (*Q53*) on the use of metastable ion studies to probe transition states, by Boyd and Beynon (*Q6*) on the determination of gaseous ion thermochemistry from measurements on metastable ions, and by Franklin (*Q20*) on energy partitioning in the products of ionic decomposition.

Fragmentations of metastable ions, free from stable ions which constitute the normal mass spectrum, are observed by scanning the accelerating voltage and the electric and magnetic sector voltages in various combinations. These techniques are now commonly available on commercial instruments and have been critically discussed (*Q7, Q34, Q40, Q42, Q52*). The information obtainable has been represented graphically on a 3-dimensional surface (*Q38*). The following ions can be measured: (a) all precursors to a given product ion (e.g., from a high-voltage scan), (b) all product ions from a give precursor (e.g., metastable-ion-kinetic-energy, MIKE, spectra) and (c) all decompositons in a given field-free region (e.g., IKE spectra). Even reactions occurring over a range of scattering angles may be studied (*Q19*). T is readily measurable on instruments of different geometry and appropriate choice of "linked" scans may resolve overlapping metastable peaks (*Q17, Q46*). However, linked scans commonly lead to loss of information on T (*Q7, Q34, Q42, Q52*) and may yield artifact peaks (*Q44*). The most important use of linked scans is in detailed fragmentation pattern elucidation and in isotopic labeling studies.

Beynon and Cooks, pioneers of IKE spectrometry, have reviewed instrumental aspects and development of the technique (*Q2*). It is shown that the basic measurement of T can be used to study unimolecular, ion–molecule and ion–surface reactions; and it is emphasized that an IKE spectrum yields useful analytical information, particularly where collisional activation is employed. The evaluation of T may be compromised by instrumental factors (as with the measurement of other energy values in mass spectrometry, e.g., appearance potentials) and graphical corrections can be applied (*Q1*). Computer techniques may aid the evaluation of metastable peak shapes and it has been shown that a Monte Carlo method computes similar shapes to the integration method (*Q27*).

Williams and Bowen have carefully demonstrated that T can be used, along with ΔH_f data, to deduce the transition state for a decomposition. For example, the overall reaction $CH_3CH_2CH{=}N^+HCH_3 \rightarrow C_2H_4 + CH_2{=}N^+HCH_3$ occurs with a T value of 46 kJ mol^{-1} (*Q54*). The primary ion $^+CH_2CH_2CH_2NHCH_3$, which decomposes to products with an enthalpy loss of 142 kJ mol^{-1}, is implicated as the reacting structure since about one third of available energy is channeled into translation in analogous ionic reactions. A detailed 5-step pathway, including the individual potential surfaces, was determined for C_2H_4 loss from $(CH_3)_2C{=}O^+H$, from isotopic labeling studies and T and ΔH_f measurements (*Q3, Q32*). For some initial structures of the homologous $C_4H_9O^+$ ion, an isomerization reaction is the rate-limiting step for decomposition, and evaluation of the potential surface permits correct predictions about metastable peak widths to be made (*Q5*). Cooks et al. have used MINDO/3 calculations and measurements of T to determine the potential surface for H_2 loss from $C_3H_5^+$. Two tight transition states are identified which channel the reverse activation energy largely into translation (*Q36*). The above examples illustrate that reaction mechanisms and transition states involving metastable ions can now be evaluated in detail (see also *Q4, Q9, Q23, Q28, Q29, Q33, Q43*). Deuterium isotope effects may also be used for this purpose and it has been continually found that k_H/k_D is high for low-energy metastable ion reactions (*Q48, Q49*).

It has been suggested that the "earliness" or "lateness" of the activated complex is another factor influencing the value of T, but this interesting hypothesis is difficult to verify experimentally (*Q23*). Excited states have been implicated from small differences in T in the reactions of a series of 4π-electron hydrocarbons (*Q45*). A comparison between T obtained for reactions of parent ions generated under EI and FI conditions constitutes a test of the QET and in certain cases the considerable differences between T (EI) and T (FI) suggest decomposition over different energy surfaces (*Q14*). T has also been measured for decomposition following CI (*Q10, Q31*) and for negative-ion reactions (*G8, G13*).

Metastable ion abundance ratios for competing processes continue to be utilized as a parameter for ion structure identity (*Q8, Q13*) and even for relative proton affinities of molecules (*Q12*). However T for *one* reaction can be used as a simple characteristic of ion structure. Thus different $C_6H_6O^+$ ions were identified from various precursors by their different T values for CO loss (*Q25*), whereas a series of $C_6H_5CO^+$ ions appear to have a common structure from their constant T values for CO loss (*Q15, Q24*). T for the *formation* of the benzoyl ion from $C_6H_5COX^+$ increases almost linearly with the uncorrected ΔH_f of the benzoyl ion (i.e., also with the nonfixed energy) (*Q15*). In this reaction, the product translational energy distributions differed widely and the profile appears to relate to the reaction mechanism (*Q16*, see also *Q26*). The application of statistical phase space theory to product translational energy distributions has been discussed at length (*N3, N5, N15*).

Metastable peak shape analysis sometimes reveals composite structure and identifies competing mechanisms (*Q19, Q30, Q47, Q51*) and a temperature effect on T has revealed a composite metastable peak (*Q41*). Deuterium labeling often augments the information gained (*Q18, Q30, Q51*) and in certain cases (e.g., from the peak shape analysis of dimethoxytoluenes) (*Q18*), structural information is obtained. Measurements on the $C_8H_8O^+$ cations from tetralol sound a cautionary note on the literal interpretation of data on T and metastable ion intensities (*Q22*).

Metastable spectra have also been employed in chemical analysis. Gallegos has described a neat method in which a mixture of structurally related compounds is analyzed initially on the probe (*Q21*). The requirement is for an abundant common ion which evolves directly from the respective molecular ions. For example, m/z 217 is a strong feature in the spectra of steranes and a high-voltage scan indicates all the parent ions yielding this ion. Cooks et al. have shown that since the MIKE spectra of parent ions of different mass may be determined, pure collision-induced MIKE spectra of mixture components can be obtained (*Q35, Q37*). This method is sensitive and applicable to partially isotopically labeled compounds. McLafferty and Bockhoff have adopted a similar theme (*Q39*) and report a sensitive analysis of complex mixtures. The techniques described by both sets of authors show promise for the replacement of GC/MS analysis in certain cases (*Q35, Q39*, see also *K11, I20*). It is also evident that there is scope for varying the ionization method in mixture analysis by metastable methods (*I20, K11, Q35, Q39, Q46, Q50*).

Isomerization Reactions of Organic Ions. It is an established fact that many organic ions undergo isomerization reactions on the time-scale of the mass spectrometer. Evidence has been accumulated over several years from a variety of techniques, e.g., metastable ion studies (including abundance ratios and translational energy releases), heat of formation measurements, molecular orbital calculations, isotopic labeling studies, collision induced decompositions, photoionization threshold measurements, photodissociation spectroscopy,

ion/molecule reactions (particularly via ICR spectrometry), and kinetic studies (e.g., FIK measurements. These techniques are covered in sections above.

It might be considered disturbing that a highly successful structural technique such as mass spectrometry should be subject to this "blurring" of structural information. However, the following factors are important: (1) the extent of isomerization is dependent on internal energy and the short-lifetime (high-energy) reactions observed in the ion-source frequently occur without prior rearrangement; (2) alternative ionization techniques to electron-impact may minimize isomerization; and (3) hydrogen rearrangements are more common than skeletal rearrangements and the former is much less likely to diminish structural information.

Two isomerizing systems studied extensively are the benzene and toluene molecular ions and their respective isomers. The situation in the benzene ion appears to be complex and isomerization between excited benzene ions and linear diyne isomers may occur prior to reaction (*H20*, see also *N6*). However, various nondecomposing linear $C_6H_6^+$ isomers studied in the ICR spectrometer show a different array of ion/molecule reactions to those of the low-energy benzene cations (*M27*). Isomerization is therefore not indicated at these low energies. The interconversion between various $C_7H_8^+$ ions has been investigated both theoretically (*O10*) and experimentally (*H7, H25, R9*). Photoionization studies (*H25*) and MINDO/3 calculations (*O10*) indicate that the toluene molecular ion rearranges to cycloheptatriene before H elimination at threshold and photodissociation spectroscopy has identified $C_7H_8^+$ fragment ions which are structurally distinct from the above isomers (*R9*). Rearrangements in substituted toluene ions have been investigated (*H10, J24, Q18*) and increased substitution appears to minimize isomerization (*Q18*). Skeletal rearrangement reactions prior to decomposition have been reported in a variety of aromatic molecular ions (*Q25, R1, R6, R21–R23*). These reactions include a C_6H_5 migration (*R1*) and a new skeletal rearrangement in the mass spectra of substituted *p*-toluic acids (*R6*).

Isomerization reactions in aliphatic hydrocarbon molecular ions have been extensively studied, particularly by Levsen et al. (*I5, I6, R17*). These reactions have been generally discussed in terms of the relative heights of barriers for decomposition and isomerization. The model is used to explain the reduced tendency for radical hydrocarbon ions to rearrange compared with even-electron ions (*R17*). A combination of CA and FIK spectroscopy (among other techniques) has shown that interconversion of nondecomposing linear octene ions is incomplete, whereas decomposing molecular ions have isomerized to a mixture of structures 1 ns after ionization (*I5*). Isomerization prior to decomposition in homologous hydrocarbon ions becomes more pronounced with decreasing molecular size (*R17*). This conclusion is borne out by the CA spectra of isomeric pentenes and hexenes (*K17*). The rearrangement and decomposition of various $C_4H_8^+$ ions have been repeatedly studied (*H19, I14, K16, N4*). CA spectra of several $C_4H_8^+$ isomers are characteristic and distinguishable, which indicates that the nondecomposing ions do not isomerize (*K16*).

The explanation of atom "scrambling" within molecular ions is closely related to the discussion of isomerization reactions outlined above, since loss of positional identity of isotopically labeled atoms necessarily occurs via interconversion between isomeric structures. There has been considerable speculation during the past decade concerning the mechanism for scrambling in ionized benzene. SCF MO calculations have now shown that this process can occur via a 1,2-proton shift, with an activation energy of 1.86 eV (*R10*). Atom randomization reactions have been investigated in other aromatic molecular ions (*R2, R13, R24, R25*) and the situation is frequently complex. Hydrogen and carbon isomerization reactions in aliphatic hydrocarbon molecular ions have been widely studied, e.g., in propane (*N20*), propene and cyclopropane (*R11*), octenes (*I5*), dodecane (*R16*), and cholestenes (*R7*). As a general rule, scrambling appears to be less prevalent in the larger cations. For example, alkyl radical elimination from the dodecane molecular ion occurs in low-energy processes primarily via a simple C–C bond split (*R16*) and isomerization does not occur in ^{13}C-labeled cholestenes (*R7*).

It has become evident from theoretical and experimental studies that molecular ions fall into several categories according to their tendency to rearrange, namely (1) Non-decomposing ions. Some or none of these ions isomerize, depending on whether the activation energy for isomerization is less or greater than that for fragmentation. These ions may be studied by CA and ICR. (2) Low-energy decomposing ions. Where isomerization occurs it is usually most prevalent in these ions due to the tight transition states for rearrangement. Metastable ion studies, ΔH_f measurements and MO calculations are employed for study in this energy range. (3) High-energy decomposing ions. These ions tend to decompose without rearrangement and are conveniently investigated via EI or FI studies.

The situation regarding isomerization in fragment ions is generally less clear, since the fragmentation parameters of the precursor ion(s) must be considered. The detailed analysis of potential surfaces, employed by Williams and Bowen, has proved to be an effective means for elucidating carbonium ion rearrangements (*Q3–Q5, Q53, R3, R4*, see also section on metastable ions above). Several authors have investigated isomerizations in CH_3O^+ and $C_2H_5O^+$ (*H1, L4, Q4, R18*). There is a high-energy barrier for interconversion between CH_3O^+ and CH_2OH^+ (*Q4*). Isomerization reactions in the related ions, CH_3S $C_2H_5S^+$, and $C_3H_7S^+$, have been investigated by CA spectroscopy (*R8, R19, R20*).

Isomerization reactions of alkyl hydrocarbon ions both in solution and in the gas-phase have been reviewed (*R14*). In some cases, solvent effects are small. Other even-electron hydrocarbon ions studied include $C_7H_7^+$ (*O6, R12*), $C_6H_7^+$ (*H9, R5*), and $C_4H_9^+$(*R15*). Carbon atoms become completely randomized in the *tert*-butyl cation (*R15*).

In conclusion, it should be emphasized that where isomerization does occur after electron-impact, alternative techniques may be employed to minimize the occurrence. For example, fast decompositions following FI frequently occur without prior rearrangement (*I9*) and the value of CI in this respect is demonstrated by its increasing use to distinguish between stereoisomers (*J9, J10, J16, J23, J24, J30*).

BIO-OLIGOMERS AND THEIR CONSTITUENTS

Amino Acids, Peptides, Proteins, and Sequencing. The chemical ionization (CI) mass spectra (reagent gas H_2) of α-amino acids have been determined and compared with CH_4-CI mass spectra. The H_2-CI spectra show a much lower MH^+ abundance and increased abundances of fragment ions formed by sequential fragmentation of MH^+. The latter has potential advantages in determining the structure of R in $RCH(NH)_2COOH$. The CH_4 and H_2-CI mass spectra of β-alanine, 3-aminobutyric acid, 4-aminobutyric acid and 6-aminohexanoic acid also have been determined. For the β-amino acids, the dominant fragmentation of MH^+ is sequential loss of H_2O and ketene, while, for the terminal amino acids, MH^+ fragments by loss of both NH_3 and H_2O. Using both CD_4 and D_2 as reagent gases, it has been found that there is substantial deuterium retention in the ions originating from fragmentation of MD^+. The results are not consistent with protonation at a specific site, but rather indicate that there is extensive intramolecular proton transfer in MH^+ prior to fragmentation (*S61*). Gaffney et al. (*S12*) have used CI with NH_3 for study of evaporation of α-amino acids. The CI mass spectra of *N*-acetyl propyl esters of 17 natural amino acids with CH_4 and He as reagent gases have been reported. Such a technique appears to be an invaluable tool to study by mass fragmentography either amino acid metabolism or amino acid incorporation in proteins, since the base peak can be a very specific ion 1000 or more times larger than in electron impact (EI) (*S40*). Chemical ionization has also been applied for rapid and quantitative analysis of amino acids in blood (*S23*). Benninghoven and Sichtermann used secondary ion mass spectrometry for biologically important compounds; the technique is an especially advantageous one for analysis of nonvolatile compounds including underivatized amino acids (*S3*).

The negative ion mass spectra of *p*-nitrobenzoyl derivatives of amino esters exhibit pronounced molecular anion and characteristic fragmentation. Fragment anions observed in the spectra of *o*-nitrobenzoyl analogues arise by various interactions between the nitro and amino ester groups. No fragmentation occurs for the *m*-nitrobenzoyl derivatives (*S58*).

The formation of carboxylate anions from *N*-acetyl-*p*-nitrobenzoyl amino esters has been observed by Brown and Chan (*S4*). Electron impact (*S38*) and field desorption (*S54*) mass spectrometry have been used for analysis of 3-phenyl-2-thiohydantoins (PTH) of amino acids produced during automated Edman degradation of polypeptides. Two main advantages of FD technique for this purpose can be emphasized: (1) excellent sensitivity and (2) high molecular ion intensity and uncomplicated fragmentation even in cases where EI mass spectrometry fails to exhibit a molecular ion. Amino acid thiohydantoins were identified utilizing EI and CI mass spectrometry (*S59*). Fluorescamine derivatives of 17 of the naturally occurring amino acids have been studied using EI mass spectrometry. Fragmentation processes of fluorophors were proposed and supported by accurate mass measurements and stable isotope incorporation (*S56*). The fragmentation of various volatile derivatives upon EI has been studied for ultra-microdetermination or the selective identification of amino acids by mass fragmentography (*S16, S17*). Using mass fragmentography of *N*-trifluoroacetyl-L-prolyl *n*-butyl esters monitored at *m/e* 166, about 100 pg of amino acids can be detected (*S17*). Chemical ionization mass spectrometry of *N*-benzoyl-α-amino acid methyl esters demonstrates that the formation of the $(M + H - MeOH)^+$ ions is strongly affected by the degree and type of substitution at α-carbon. The extent of the formation of this ion closely resembles that of the activated esters in condensed phases (*S13*). The mechanisms of some fragmentations of methionine upon Curie-point pyrolysis have been studied with the aid of deuterium labeling. The products have the same nominal mass but essentially differ in elemental compositions compared with the ions generated by electron impact (*S45*). Detection of tryptophan metabolites in physiological fluids through absorption on XAD-2 followed by desorption, conversion into *n*-pentafluoropropionyl derivatives and single ion monitoring at *m/e* 276 (characteristic for indoles) or *m/e* 438 (characteristic for 5-hydroxyindoles) has been described by Segura et al. (*S55*). The EI mass spectra at 70 eV of *N*-acetyl-*O*-methyl esters of hystidine, tryptophan, and cystein have been reported by Felker (*S9*). Roessler and Hesse investigated the origin of the $(C_5H_{10}N)^+$ ion— the base peak in the mass spectrum of lysine methyl ester (*S50,S51*). The results can be most easily explained by postulating an ion structure in which both nitrogen atoms are in identical positions. The heptafluorobutyryl methyl ester derivatives of thyroid hormones exhibit interpretable EI mass spectra with well defined molecular ion peaks. Subpicogram detection limits are attained in the analysis of these derivatives with capillary column gas chromatography–mass spectrometry (*S44*). A ninhydrin positive substance isolated from the culture filtrates of *Streptomyces tendae* (Tu 901) was identified as 3-cyclohexenylglycine by GC/MS of TMS derivative and *N*-trifluoroacetyl methyl ester (*S20*). A comparison of EI and FI mass spectra of some 2,5-diketopiperazines was presented by Szafranek et al. (*S60*).

Sequencing of polypeptides and proteins by combinations of gas chromatography and mass spectrometry has been extensively reviewed by Arpino and McLafferty (*S2*), Falter (*S8*), Morris and Dell (*S26*), and Nau (*30*); the related literature up to 1976 was included. A generally applicable strategy for polypeptide sequencing has been developed by Biemann and his co-workers (*S14, S18, S31–S37*). This approach involves cleavage of a large peptide to a mixture of small peptides whose individual amino acid sequences are then established without their prior separation. This is attained by transformation of the peptides into the corresponding *O*-TMS polyamino alcohols through reduction of the *N*-acylated peptide esters with $LiAlD_4$, followed by treatment with Me_3SiNEt_2. These peptide derivatives possess excellent GC properties. The identification of these compounds either manually or with aid of the computer is based on three sets of data automatically generated after GC/MS/computer analysis: (i) mass spectra, which exhibit sequence determining ions of high abundance, (ii) selected ion records which allow efficient location of peptide derivatives in the gas chromatogram as well as resolution of incompletely separated fractions, and (iii) retention indices, which can be calculated from values assigned to each amino acid residue. This sequencing strategy was evaluated using 0.4 to 1.4 mol peptides with known structures and then applied to peptides above 40 amino acids long. The primary structures of the carboxypeptidase inhibitor from potatoes (*S34*) and subunit I of monellin (*S14*) have been elucidated this way, and subunits A and C of monellin have yielded unique sequences of 44 and 50 amino acids which completed the 94-unit protein sequence (*S15*). Special methods of derivatization were elaborated for asparagine- and glutamine-containing peptides to enable application of the above outlined general strategy in this particular case (*S32–S34*).

The other approaches to polypeptides sequencing were also investigated. The amino acid sequence of a polypeptide can be deduced by an identification of all the dipeptides obtained from a dipeptidylaminopeptidase I hydrolysate of the original polypeptide and its des-*N*-terminal amino acid derivative. The components of such dipeptide mixtures can be readily identified from the CI (helium as gas reagent) mass spectra of their *N*-ethoxycarbonyl methyl ester derivatives without prior separation. The pyrolytic conversion of *N*-protected peptide dimethyl trideuteromethyl anilinium salts to their methyl esters on the direct insertion probe of a mass spectrometer was found to be most suitable for the derivatization of such dipeptide mixtures (*S57*). Desiderio and his co-workers used acetylacetonyl as the *N*-protective group for dipeptide methyl esters (*S10*). GC/MS properties of these derivatives were found to be suitable for identification of components in a complex mixture of dipeptides and unambiguous identification was achieved even for unresolved GC peaks. A simple straightforward method for differentiating asparaginyl (or glutaminyl) dipeptides from aspartyl (or glutamyl) dipeptides was described by the same research group (*S65*).

N-Acyl-*O,N*-permethylated oligopeptides of up to 5 amino acid residues are sufficiently volatile for GC separation. The gain in sensitivity was achieved from use of open tubular GC columns together with CI mass spectrometry (*S46*). The reaction products of trifluoroacetic anhydride with peptide amides can be analyzed by GC/MS; the mass spectra exhibit intense $M^{+\cdot}$ ions and allow the assignment of the amino acid sequence (*S7*). Mass spectra of underivatized hexa- and heptapeptide amides related to "Substance P" have been obtained with EI mass spectrometry using sample vaporization from a tungsten wire by the technique of rapid heating, proton transfer ionization using ammonia, and photoplate recording of spectra. These spectra are readily interpreted in terms of amino acid sequence (*S1*). DeJongh et al. (*S5*) reported that the permethylated *N*-succinyl derivatives of peptides can be readily prepared on a small scale, are volatile, and show characteristic fragments in their mass spectra, abundant peaks being observed in the high mass region due to loss of MeO· from the *N*-succinyl carbomethoxyl group as well as from the *C*-terminal carbomethoxyl group. Ions characteristic of the sequence and of individual amino acids are present and molecular weight can be detected from the relatively abundant ion at $(M - MeO^+)$ and from the weak M^+ ion. The DADI and defocusing spectra have been recorded for a number of peptides and their equimolecular mixtures; the $M^{+\cdot}$ ion of each peptide is decomposed to a series of daughter ions giving the very specific pattern of a DADI spectrum in which both the nature and the position of the amino acid residue are reflected (*S48*). The analysis of metastable ions decomposition by DADI and defocusing methods allows unambiguous identification of the peptide mixtures as well. Field and his coworkers (*S27, S28*) have developed routine protocol for sequencing peptides by CI mass spectrometry with samples as small as 10 nmol, which includes isolation of peptides by column chromatography or paper electrophoresis, acetylation, *N,O*-permethylation and determination of the CI (isobutane) mass spectra during fractional distillation of the peptide mixture from a direct insertion probe; a GC/MS data system is then used to select spectra at the maximum sample flow of each component of the mixture, the selected spectra being processed by the sequence determination program. The same research group reported that *C*-methylation occurs in peptides derivatized for sequencing by mass spectrometry (*S29*). Frick et al. (*S11*) discussed peptides derivatization by methylation and methanolysis, and their structure analysis by field desorption mass spectrometry. The computer program for sequencing of linear peptides based on amino acid analysis and high resolution mass spectral data is described; the submolecular group analysis was utilized for identification of sequential ions from the high resolution mass spectra (*S24*).

Mass spectrometry was also used for sequencing of the peptides containing aminomethylphosphonic acid residues (*S64*); enkephalines— the brain's natural opiates (*S25*); myoglobin from an odontocete *Tursiops truncatus* (*S49*); cyclodepsipeptides (pimaydolide) (*S53*) and *Alternaria mali* toxins (*S62*); a new depsipeptide from *Pithomyces chartarum* (*S47*); a peptide antiobiotic, stenothricin (*S19*); and for elucidation of which amino groups of lysine take part in a peptide bond with a neighboring amino acid residue (*S52*). Okada and Kawase (*S39*) have applied mass spectrometry for differentiation of α- and γ-linkages in glutamyl oligopeptides. Some attempts were undertaken to apply field desorption mass spectrometry to polypeptide analysis. The low resolution field desorption mass spectrum of glucagon, a 29 amino acid residues underivatized peptide, shows the fragments containing no more than 18 amino acid moieties (*S63*). Field desorption mass spectra of hypothalamus peptide hormones and related compounds were also published (*S21*).

Structure determinations of several members of the peptaibophol class of peptide antibiotics have been carried out by Rinehart and co-workers using an impressive arsenal of complementary mass spectral techniques, viz., FDMS and GLFDMS, high resolution FD and EI MS, and GC/HREIMS. This group has established the structures of antiamoebin I (*S42*), emerimicin III and IV (*S43*), and alamethicins I and II (*S41*).

Marino and Malorni (*S22*) have investigated the relative abundance of the sequence ions and found that the *N*-terminal protective group had a pronounced effect on peptide fragmentation; the very low ionization potentials of this group are useful in the sequencing of peptides by mass spectrometry.

Dell and Morris have shown that homologous proteins can be rapidly screened using an approach involving nonspecific digestion using elastase, and minimal purification of peptides followed by sequencing of peptide mixtures. The enzymes chloramphenicol transacetylase and a copper-containing respiratory protein from *Pseudomonas fluorescens*, bio-type 6, were used as illustrations (*S6*).

Purines, Pyrimidines, Nucleosides, Nucleotides, and Nucleic Acids. The first adiabatic ionization potentials of some purine and pyrimidine bases and their analogues have been measured by photoionization mass spectrometry (*T21*). Young has described a highly selective method for the detection and identification of cytokinins at submicrogram levels in plant extracts. The partially purified preparations are methylated by the Hakomori procedure and the permethylated derivatives then analyzed by GC/MS using multiple ion detection (*T33*). The fragmentation of N^6-(3-methyl-2-butenyl)adenosine and related cytokinins (*T11*) and pertrimethylsilyl and permethyl derivatives of glucosides of zeatin and 6-benzylaminopurine (*T17*) has been studied in detail.

Glucosyl zeatin and glucosyl ribosylzeatin have been identified from *Vinca rosea* crown gall (*T20*). Three ribonucleosides responsible for cytokinin activity in *Euglena gracilis* var Bacillaris tRNA have been shown to be 6-(3-methyl-2-butenylamino)-9-β-D-ribofuranosylpurine, 6-(4-hydroxy-3-methyl-cis-2-butenylamino)-9-β-D-ribofuranosylpurine, and 6-(4-hydroxy-3-methyl-2-butenylamino-2-methylthio)-9-β-D-ribofuranosylpurine (*T29*).

Structures of discadenine, a spore germination inhibitor from the cellular slime mold *Dictyostelium discoideum* (*T1*), the adenine containing product of chemical transglycosylation of "octosyl acid" (*T2*), and nikkomycin, a new inhibitor of fungal chitin synthesis (*T8*, *T14*), have been elucidated with the aid of EI mass spectrometry.

McCloskey and Nishimura (*T18*) have recently reviewed the occurrence and structural variations of all known modified nucleosides in transfer RNA (tRNA). *Streptomyces cacaoi* has been shown to contain a novel class of nucleosides— anhydrooctosyluronic acid derivatives of 5-substituted uracils (*T7*). Negative ion mass spectra of trimethylsilyl, trifluoroacetyl, and *O*-*o*-nitrobenzyl derivatives of nucleosides have been compared with existing respective positive ion data (*T27*). Sterically crowded trialkylsilyl derivatives of nucleosides have been recorded, viz., *tert*-butyldimethylsilyl, *cyclo*-tetramethylene-*tert*-butylsilyl, and *cyclo*-tetramethylene-isopropylsilyl derivatives (*T22*). Loss of the bulkiest group yields the most abundant fragment in the high mass region.

Field desorption mass spectrometry has been utilized for characterization of a variety of nucleosides, 2′-deoxyribonucleosides, and their alkylated derivatives (*T10*). A typical spectrum contains a strong molecular ion and smaller peaks representing the constituent base and sugar. In some cases cluster ions are also found. The procedure has been used to elucidate structures of products of the reaction of the mutagen 2-chloroethyl ethyl sulfide with deoxyadenosine and deoxyguanosine. Initial efforts to gain mass spectral data of free di- and trinucleotides using the ^{252}Cf plasma desorption techniques have been reported (*T19*). For ApUpG, ions were observed in three distinct mass ranges corresponding to mono-, di-, and trinucleotide ions. Neither positive nor negative molecular or quasimolecular ions were detected, although peaks which may include one or more Na or K were observed. Photoionization mass spectra of hydroxyalkyl pyrimidines have also been reported (*T26*).

The reaction products of the antitumor agent 1,3-bis(2-chloroethyl)-1-nitrosourea with poly(C) and poly(G) have been shown using EI to be 3-(β-hydroxyethyl)GMP (*T16*).

Studies aimed at elucidation of the molecular structures of the covalent adducts of several carcinogens with RNA and DNA have been reported. Determination of the structure of the major adduct formed with DNA by aflatoxin B_1 activated in vitro was achieved with considerable information from FD-MS and high resolution MS. The adduct representing 90% of the in vitro binding was shown to be 2,3-dihydro-2-(N^7-guanyl)-3-hydroxyaflatoxin B_1 (*T9*). The major guanosine adduct formed with poly(G) and racemic 7,8,9,10-tetrahydro-7,8-diol 9,10-epoxide of benzo[*a*]pyrene in vivo has been determined using ^1H NMR and high resolution mass spectrometry of the diacetate, diacetonide (T12). Covalent binding of the benzo[*a*]pyrene metabolite (±)7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene to calf thymus DNA in vitro has been carried out recently. Isolation by HPLC yielded microgram quantities of adducts which were identified as the exocyclic amino products of deoxyguanosine using EI high resolution mass spectrometry on both the permethylated and pertrimethylsilylated derivatives (*T28*). 7,12-Dimethylbenz[*a*]anthracene 5,6-oxide has been shown to bind covalently to 2′-position in the ribose moiety of guanosine (*T13*).

Schulten and Schiebel (*T23*, *T24*) and Budzikiewicz and Linscheid (*T3*, *T4*) have applied FD mass spectrometry for sequential analysis of oligonucleotides. Dinucleoside phosphates exhibit a typical fragmentation which offers sequential information, viz., cleavage yielding a nucleoside-2′:3′-cyclophosphate and nucleoside moiety. No sequencing information can be obtained this way for deoxyribo series and for dinucleotide-2′:3′-cyclophosphates. The other approach to the sequence analysis of oligodeoxyribonucleotides has been used by Wiebers and his co-workers (*T5*, *T6*, *T30*). Their strategy is based upon the analysis of intact underivatized oligonucleotides by mass spectrometry followed by interpretation of the mass spectral data by a computerized pattern-recognition technique. The method permits the reconstruction of a sequence of tetranucleotides.

Polynucleotides have been studied by pyrolysis FI and FD mass spectrometry (*T25*). Six major components of a mixture of the pyrolysis products of deoxyribonucleic acid have been identified by means of collisional activation spectrometry (*T15*).

A mass spectrometric method is described for the detection and identification of unusual nucleotide residues present in DNA molecules (*T31*, *T32*).

Carbohydrates. The procedure for GC/MS identification of all possible methyl ethers of D-mannose has been developed (*U33*). The methyl ethers were converted to peracetylated aldononitriles prior to analysis. The procedure has been used for structure elucidation of dextranes (*U34*) and extracellular D-mannans from yeasts (*U35*).

Mass spectra of underivatized D-glucose and sucrose obtained by Li^+ ion attachment in a high electric field have been described (*U10*). The mass spectrum of glucose contains only $(M + Li)^+$ ions, whereas the mass spectrum of the thermally labile sucrose shows numerous peaks resulting from (Li^+) ion attachment to thermal decomposition products. The mass spectra of trifluoroacetates of methyl hexopyranosides and their partially deuterated derivatives were measured (*U1*). The trifluoroacetyl derivatives were found to be very useful

for identification of some stereoisomeric hexoses. The mass spectra were characterized by abundant peaks in the high mass range, the presence of a recognizable molecular ion, and sensitive spectral differences due to different stereoisomers. Glucose, galactose, and mannose were distinguished by comparing the intensities of the fragment ions due to the loss of trifluoroacetyl groups or cleavage of the pyranose ring; α- and β-anomers were distinguished by differences in the abundance of fragment ions produced by the loss of glycosidic methoxyl groups. Negative molecular ions of peracetates of pento- and hexopyranoses eliminate ketene, $CH_3CO\cdot$, CH_3COOH, and acetic anhydride; intensities of fragment ions depend on structure and stereochemistry of the molecules (*U19*, *U40*). The mass spectra of negative ions of methyl ethers of glycopyranosides are insensitive to stereochemical effects (*U3*); MeO^- ions have the highest intensity, while other peaks correspond to elimination of H·, MeO·, and MeOH from the molecular anion. The electron impact mass spectra of the methyl α- and β-glycosides of axenose, of a number of derivatives, and of mycarose, display substantial differences, characteristic of their stereochemistry; the observed differences were attributed to the presence of an intramolecular hydrogen bond between the hydroxyl group at C-3 and the oxygen atom of the methoxy group in the methyl α-glycosides of axenose and mycarose (*U11*). Monosaccharides were detected in tannin hydrolysates from ink of ancient manuscripts (11th to 16th century) by means of GC/MS of their trimethylsilyl derivatives at the nanogram level (*U2*). The EI mass spectra of acetates of certain *C*-glycopyranosides have been recorded; the plausible explanation of some peculiarities in their behavior upon electron impact was proposed (*U31*). The mass spectra of the *O*-acetyl and *O*-trimethylsilyl derivatives of D-glucal and D-xylal have been determined and deuterium labeling was used for elucidation of the fragmentation mechanisms (*U39*). The same labeling technique has been used in reinvestigation of the fragmentation mechanism of methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside; as a result, the structures of some ions arising upon electron impact have been revised (*U43*). Mass spectra of methyl ethers of methyl α-L-rhamnopyranoside have been discussed by Kovačik et al. (*U21*). Otake and Sonobe (*U26*) have presented data on GC/MS of some methyl ethers of methyl α-D-fucopyranoside. Fragmentation of methyl(methyl *O*-acetyl-*O*-methyl-α-D-gluco- and -galactopyranosid)uronates has been studied at 70 and 12 eV by Kovăcik et al. (*U20*). At 12 eV, the spectra are simpler and easier to interpret. The number and location of methyl groups in methyl(methyl *O*-acetyl-*O*-methyl-hexopyranosid)uronates can be determined. The procedure is particularly suitable for GC/MS of the uronic acid portion of methanolysates of methylated biopolymers and other substances containing uronic acids.

Many of the stereoisomers of methylated hexitol acetates having the same arrangement of *O*-methyl and *O*-acetyl groups yield markedly different CI mass spectra. The observed differences are reproducible. Hence, CI mass spectrometry when combined with GC and EI mass spectrometry is of value in identification of the methylated alditol acetates (*U25*). The chemical ionization mass spectrum of methyl 2,3,4,6-tetra-*O*-methyl-β-D-galactopyranoside has been studied (*U17*, *U38*). The mass spectrum shows four abundant peaks, corresponding to the QM^+ ion and the fragment ions arising from QM^+ through elimination of one, two, or three MeOH molecules with preferential loss of MeO groups from C_1, C_3, and C_4, respectively. Close similarity between the mechanisms of QM^+ fragmentation and acid catalyzed hydrolysis was demonstrated through comparison of the CI mass spectra of anomeric permethylated galactopyranosides at different temperatures (*U17*, *U37*) and by study of the CI mass spectra of methyl ethers of deoxyhexopyranosides (*U17*, *U36*).

The permethylated methyl glycoside methyl esters of *N*-acetyl- and *N*-glycolylneuraminic acids and of *N*-acetylneuraminic acid 8-acetate have been analyzed by GC/MS. Fragmentation of the neuraminic acid derivatives in EI-MS has been studied by deuterium labeling; the results were applied in the methylation analysis of neuraminic acids from gangliosides of brain and kidney (*U30*) and sialic acid containing polysaccharides (*U4*).

The mass spectra of isopropylidene derivatives of hexofuranoses have been investigated; fragmentation mechanisms based upon results which were obtained with deuterium- (*U16*) and ^{13}C-labeled (*U32*) molecules have been proposed. The fragmentation of 1,2-*O*-isopropylidene-α-D-*glycero*-tetrafuranos-3-ulose (*U12*) and di-*O*-isopropylidene-1,2,5,6-α-D-*ribo*-hexofuranos-3-ulose (*U13*) under electron impact has been studied with the aid of deuterium and ^{18}O labeling. The effect of substituting a hydrogen atom of C_4 for a CH_3 and that of replacing the carbonyl function with cyanomethylenic substituent is also reported (*U12*). An extensive study of the fragmentation of 46 benzylidene acetals of hexopyranosides of the allo, galacto, gluco, and gulo, and manno series and some of their mono-oxidation products under EI has been undertaken by Bosso et al. (*U5*). Except for the $M^{+\cdot}$ ion which is always present [usually together with $(M + H)^+$ and $(M - H)^+$] ions formed by cleavage of C1–C2, C4–C5, and the benzylic C–O4 bonds, C1–C2, C3–C4 bonds, and C1-O5, C2–C3 bonds are observed whose abundances depend on the substituents or functional groups present in the molecule. In most cases, these fragmentations allow location of the substituents in these 1,3,6-trioxabicyclo[4.4.0]decane systems. Wiecko and Sherman have reported on the mass spectra of cyclic alkane boronates of sugar phosphates (*U41*) and sugar acetates (*U42*). The interaction of a phosphate or an acetyl moiety with boron accompanied by the loss of the alkyl radical occurs following electron beam ionization. The interaction is localized to the adjacent cyclic boronate, thus being a stereochemically sensitive probe of structure.

A new method for simultaneous determination of a reducing terminal group and component hexoses in oligosaccharides by mass fragmentography with dual-ion monitoring has been developed by Kamei et al. (*U18*). The procedure includes reduction of an oligosaccharide with sodium borodeuteride followed by acidic hydrolysis, sodium borohydride reduction of the mixture of monosaccharides formed, and acylation of resulting alditols by trifluoroacetic anhydride. The obtained mixture of trifluoroacetates was then analyzed by mass fragmentography with monitoring of m/e 645 and 646 ($M - CF_3COO$). The detection limit is 1 μg. Some novel data concerning structure determination of *N*-acetyl amino sugar derivatives and disaccharides by GC/MS have been presented by Coduti and Bush (*U8*). Gas chromatographic retention times and mass spectral fragmentation patterns were obtained for the trimethylsilyl ethers of 2-acetamido-2-deoxy-D-glucose, -galactose, and -mannose; α- and β-methyl glycopyranosides and glycofuranosides of *N*-acetylglucosamine, *N*-acetylgalactosamine 3-*O*-methyl-*N*-acetylglucosamine; β1–4 and β1–6 linked 2,2′-diacetamido-2,2′-dideoxyglucopyranosylglucoses and the glycopeptide-linkage compound 2-acetamide-1-*N*-β-L-aspartyl-2-deoxy-β-D-glucopyranosylamine. From the mass spectra of the trimethylsilyl derivatives of the free and partially methylated monosaccharides, it is possible to determine which and how many positions are methylated and whether the ring is in the pyranose or furanose form. Fragmentation patterns of the disaccharide derivatives allow detection of the linkage position. Qualitative and quantitative determination and structural analysis of various oligosaccharides from human urine using derivatization and GC/EIMS have been described in a series of papers by Lundblad and co-workers (*U14*, *U15*, *U22*, *U23*). Structural analysis of aminocyclitol aminoglycoside antibiotics by means of mass spectrometry has received further attention. The EI mass spectra of a series of underivatized aminocyclitol aminoglycoside antiobiotics have been reported and their utility in making structural assignments is discussed (*U9*). The compositions and origins of the fragment ions were confirmed by high resolution and DADI measurements, respectively. In general, the mass spectra of underivatized compounds, at least up to the pseudotrisaccharide size, were simpler to interpret and afforded more useful diagnostic information than those of their more volatile permethyl, trimethylsilyl and per-*N*-aralkylidene derivatives. A comparative study of CI (isobutane) and FD mass spectra of aminoglycoside antibiotics gentamycins (individual components and commercial mixtures) has been presented by Parfitt et al. (*U27*). The CI spectra exhibit some fragmentation, but under optimum FD conditions little glycosidic cleavage is observed and $(M + H)^+$ ions dominate the spectra. Chizhov, Dougherty, and their associates (*U7*) studied CI mass spectra (isobutane and isobutane/ammonia as the reagent gases) of the 6 permethylated glycopyranosyl alditols and 2 permethylated biosylalditols. Intense peaks corresponding to $(M + H)^+$ or

$(M + NH_4)^+$ were observed in all cases. In the isobutane CI spectra, the ratios of abundances for the alditol ions that are formed by cleavage of the glycosidic bond on the alditol or glucosyl side of the glycosidic oxygen depend strongly on the position of the glycosidic linkage. Determination of the position of the glycosidic bond is possible this way. The same is valid concerning biosylalditols. Application of FD mass spectrometry to oligosaccharides has been discussed by Prome and Puzo (*U28, U29*). Addition of alkaline salts (NaI or KI) greatly increases the sensitivity, and catonized molecular ions are observed. The influence of the molar ratio sugar/salt on the nature and relative intensity of the desorbed species has been studied and optimized. The technique has been applied to the FD MS of several oligosaccharides; di-, tri- and tetrasaccharides exhibit intense $(M + Na)^+$ ions in the presence of NaI and only a few fragment peaks are observed. The method has been used successfully for analysis of mixtures of oligosaccharides.

Some triterpenic saponins of oleanane type (*U16*) and glucuronides of cannabinoids (*U24*) have also been characterized by means of EI mass spectrometry.

Complex Lipids. Chemical ionization mass spectrometry in combination with GC and computer systems (*V12*) was successfully applied to analysis of various lipids. Triglycerides have been analyzed by CI mass spectrometry using a direct inlet system and ammonia as the reagent gas (*V11*). The EI mass spectra of naturally-occurring neutral glycerolipids of the ether type have been measured and the peaks which could be used in mass spectrometric analysis of natural ether lipids have been selected and tabulated (*V16*). Trimethylsilyl derivatives of 1-alkyl-2-acylglycerols have been studied by GC-MS and the following points have been noted as characteristic of their fragmentation pattern: (i) ions $(M - 15)^+$ and $(M - 90)^+$ are 14 mass units less than those of the corresponding diacyl derivatives; (ii) the base peak is m/e 130; (iii) ions at m/e 314 and 342 are characteristic of the trimethylsilyl derivatives of hexadecyl and octadecylglycerols, respectively (*V17*). The mass spectra of alk-1-enyl-2,3-diacyl-, alk-1-enyl-2-acyl-, alk-1-enyl- (*V2*) and alk-1-enyl-2-acyl-3-trimethylsilylglycerols (*V18*) have been also reported. It was noted that these mass spectra permit complete establishment of the structures of the lipids of the above types.

Glycolipids of various *Mycobacteria* have continued to attract the attention of several research groups. Batrakov et al. (*V1*) isolated unusual acidic glycolipid from *M. paraffinicum* and have elucidated its structure with the aid of high resolution mass spectrometry as 2-*O*-octanoyl-2′,3-di-*O*-decanoyl-6-*O*-succinoyl-α,α-D-trehalose. Two other lipids derived from trehalose have been isolated from *M. tuberculosis* and characterized by means of mass spectrometry (*V5, V19*).

Field desorption mass spectrometry has been extensively applied to investigation of highly polar intact phospholipids (*V15, V20, V21*). The behavior of a wide variety of phospholipids and related material (phosphatidylcholines, both acyl and alkyl, phosphatidylethanolamines, phosphatidic acids, the corresponding lysocompounds, glycerophosphoryl lipids, and sphingolipids) has been studied. Most of the compounds gave $(M + H)^+$ as the base peak. Problems encountered include interference from organic impurities and alkali metal ions, poor reproducibility of minor ions, and potential confusion in structural assignments caused by reaction occurring on the emitter surface prior to desorption (*V21*).

Conventional EI or CI mass spectrometry was utilized for analysis of phospholipids after degradation. Methods have been described for the analysis of phospholipid molecular species with straight or various branched chain (iso-, anteiso-, and mid-branched) fatty acids from various gram-positive or gram-negative bacteria. The procedure included: isolation of phospholipids followed by acetolysis and GC-MS of monoacetyldiglyceride mixtures formed (*V14*). The molecular species of phosphatidylethanolamine, phosphatidylglycerol, and cardiolipin of thermophilic bacterium PS3 were treated in a similar way and then subjected to GC-MS using CI with ammonia as reagent gas (*V8*).

Some novel data have been published concerning characterization of sphingolipids by mass spectrometry. The spectra of H-active glycolipid from dog small intestine, a novel difucosyl A-similar glycolipid of intestine, the major A- and B-active glycolipids of human erythrocytes, a novel difucosyl A-active glycolipid of human erythrocytes (*V10*) and the major mammalian retinal ganglioside [a sialyl-sialyl-dihexosylceramide (*V7*)] have been discussed. A comparative study of the molecular species of cerebrosides in animals and plants using GC-MS with EI or CI has been done by Hayashi and Matsuura (*V6*). Sphingosines and ceramides have been analyzed by GC-MS after preliminary conversion into cyclic methaneboronates (*V3, V4*). The methanoboronate derivatives possess excellent GC properties and give informative mass spectra; molecular ions are present in high abundance and are accompanied in the EI mass spectra by fragment ions corresponding to the acyl group and long-chain base.

Mass spectral studies of intact ganglioside derivatives have been shown to afford specific information on the type, number, and sequence of sugars as well as ceramide structure (*V9*).

Lecithins are of particular importance since they are related to the respiratory function of lung and in the pediatric field to the idiopathic respiratory distress syndrome. Ogino and co-workers have studied lung lecithins at various periods in the latter part of gestation in the rabbit by conversion to TMS derivatives of corresponding diglycerides and analysis by SIM (*V13*).

STUDIES OF BIOMEDICALLY IMPORTANT SUBSTANCES

The use of mass spectrometry in biochemistry and medicine is a recent development, but a development which will probably overshadow all other applications of mass spectrometry, to judge by its rapid growth and the range of different types of laboratories now purchasing instruments. It seems natural therefore to single this subject out for detailed discussion within this review.

Clinical Chemistry. Mass spectrometry is not used for routine analysis in clinical chemistry laboratories although the staffs of these laboratories frequently have such instruments available or have access to them when specialized analysis is required. However, there is one branch of clinical chemistry where mass spectrometry is making an impact and this is in *definitive methodology*.

The requirement for accurate methods of analysis is of growing importance in routine clinical chemistry. This is essential if published values are to be meaningful on a national and international basis, especially over a long period. Although sound clinical judgement is possible within a hospital where the laboratory results are precise but inaccurate, the situation is much improved by quantitative knowledge of the inaccuracy. In principle, this can be achieved by calibration of *routine* methods of assay against corresponding *reference* methods that are available to the laboratory and that can in turn be standardized against a *definitive* method—i.e., a method of highest proven accuracy, which is likely to be outside the scope of individual hospital laboratories. However, standards, validated by means of definitive methods can be circulated to check reference methods.

It was shown by Cali et al. (*W8*) of the National Bureau of Standards (NBS) that isotope dilution mass spectrometry (IDMS) offers a practical approach to definitive assay for selected analytes. They developed a reference method for total calcium in serum based on standard reference material calcium carbonate as primary standard. A similar method was reported by Moore and Machlan (*W14*) in which the serum concentration can be measured to within 0.2% of the true value.

Following up the initial work at NBS in calcium assays by IDMS, methods for the determination of other inorganic ions were defined and these included sodium, potassium, magnesium, lithium, chloride, and lead (*W15*). Pickup (*W16*) has developed a definitive method for the determination of phosphate and recently methods have been developed at NBS for the assay of cholesterol, uric acid, creatinine, and glucose (*W15*). The glucose analyses are being carried out with uniformly labeled ^{13}C glucose by measurement of labeled and unlabeled 1,2:5,6-di-*O*-isopropylidene-D-glucose using ions at m/e 250 and 245 (*W18*). It was found in this study that use of 6,6-dideutero-D-glucose for these analyses showed a significant (~2%) deuterium isotope effect in the measurement. Using this *definitive* method, the NBS *reference* method (hexokinase glucose-6-phosphate dehydrogenase) has been evaluated and it showed a positive bias at the lowest glucose level and small negative bias at the highest level. During the

past few years a Swedish group have developed reference methods for a series of important biochemicals, e.g., cholesterol (*W6*), glucose (*W1*), triglycerides (*W7*), cortisol (*W3*), testosterone (*W3*), progesterone (*W2*), urea (*W4*), and creatinine (*W5*) using GC/MS with stable labeled internal standards. They emphasize, however, that their methods must be considered *reference* and not *definitive* or *absolute* methods because of the unavailability of sufficiently pure reference compounds. Another reference method for cholesterol using ^{14}C cholesterol as internal standard has been published by Siekmann et al. (*W17*).

Considerable attention has been given to methods for determination of uric acid. Ismail and Dakin studied the EI mass spectrometric fragmentation of tetraethyl uric acid as a preliminary to developing an IDMS method (*W10*). However, the products were numerous and the fragmentation pattern did not permit differentiation between *N*-ethyl and *O*-ethyl substitution. A method was reported at the Xth International Congress of Clinical Chemistry, Mexico, February 1978, for the IDMS analysis of uric acid without derivatization (*W12*). This assay which uses $^{15}N_3$-uric acid as internal standard will form the basis of a definitive method. Two similar methods have been reported for the determination of creatinine using $^{15}N_2$-creatinine as internal standard (*W5*, *W13*).

Within the European Community, a Committee has been set up by the Bureau Communité de Réferênce (European Community Expert Group on Steroid Hormone Assay) to develop the use of mass spectrometry in establishment of definitive methods for steroid hormone analyses which have traditionally had extremely poor reproducibility and accuracy (*W11*). The Expert Group has been awarded approximately $180 000 for synthesis of pure stable labeled and unlabeled cortisol, estradiol-17β, and other hormones. In the United States a conference was recently held (*W9*) in Atlanta under the auspices of the DHS Center for Disease Control, the FDA and NBS to "develop a national understanding for the development of reference materials and methods (principally IDMS) for clinical chemistry". It is obvious that tremendous interest has been generated for the improvement of the accuracy of clinical chemistry methods and in the immediate future funds will be made available for the synthesis of labeled materials of sufficient purity to be used in the establishment of definitive methods using IDMS. At the present time most of the methods developed are *reference* methods since the standard material and isotope-labeled materials are not generally of high enough isotopic/chemical purity to be used in definitive methodology. However, once these materials become available, methods can be rapidly established since the experience has already been obtained in the development of the reference methods.

Although the previous paragraphs have dealt at some length with the subject that is most relevant to *routine* clinical chemistry, the analysis of individual chemical components in tissue, body fluids, etc., must be considered the principal role of mass spectrometry in human biochemistry. In the following sections, analytical studies by mass spectrometry of different suites of compounds obtained from body fluids are described preferentially, although communications reporting basic mass spectral data on the compounds themselves are also reviewed.

Organic Acids and Volatile Components of Body Fluids. The past two years have seen a rapid expansion in the number of communications relating to metabolic profiling by GC/MS. It is not necessary to discuss this topic in detail since an excellent comprehensive review of the subject has just been published (*X16*). It is useful though to describe here some of the more significant advances in this field. In terms of work-up procedures for urine, it is now accepted that DEAE-Sephadex ion-exchange methods are the only ones that ensure almost quantitative recovery of acids (*X19*, *X31*), although details of the procedure are still being hotly debated, particularly the issue of whether or not inorganic sulfate and phosphate should be removed before analysis (*X5*, *X30*). Glass capillary columns are finally finding their place in organic acid profiling, and publications by the Oslo group (*X11*, *X15*, *X17*) and others (*X18*) describe the use of this technique. Meili et al. (*X23*) have further advanced the subject by analyzing organic acids on glass capillaries coupled directly to the source of a high resolution mass spectrometer. When used in repetitive scanning mode, this is an exceedingly powerful technique but capillary GC is not accepted as desirable by all investigators in the field. Several researchers believe that suitable data processing techniques (e.g., maximizing ion) give equivalent results to data produced by capillary column analysis. The value of data improvement techniques is not in question but it is also probable that better data (e.g., obtained by capillary GC) will in turn give even better resolution when maximizing ion criteria are employed. At this stage, credit must be given to Sweeley and co-workers for their huge contribution to development of methods for separating and quantifying component mixtures (particularly of organic acids) using their MMSMET and MS-SIM programs for repetitive scanning and selected ion monitoring (*X28*). They have developed a system which uses retention indices in performing off-line reverse library searching of selected mass chromatograms from repetitive scanning GC/MS of complex mixtures. More than 100 compounds are automatically identified and quantitated. Observed precision of retention index is 0.2% and lower limit of detection is 10 ng. The GC/MS precision was 8% within duplicate detection of same sample and the linear range for quantitative analysis was 1000-fold (*X10*).

Congenital enzyme defects in organic and amino acid metabolism continue to provide some of the most interesting studies. Chalmers et al. (*X4*) describe increased excretion of lactate and pyruvate and other organic acids in an infant with pyruvate decarboxylase deficiency. Repetitive scanning data were processed using maximizing ion criteria and an impressive improvement in apparent resolution is seen. With respect to "normal" excretion of organic acids, several papers have appeared on qualitative and semiquantitative determination of organic acids in urine from newborns (*X1*, *X13*), infants (*X31*), adults (*X2*, *X10*, *X19*), and the effect of individual variation and diet on the excretion of this group of compounds (*X3*).

The technique of GC/MS has had an enormous impact on the study of organic acidurias caused by congenital enzyme defects in organic and amino acid metabolism. Up to 1977, 23 different new diseases have been described and 50–60 previously described inborn errors can be conveniently diagnosed by this technique (*X16*). Approximately half of the 200 metabolic disorders that are recognized today can be studied by such methods. Urinary organic acids have been determined in Reye's syndrome (*X14*), 3-methylcrotonyl-CoA carboxylase deficiency (*X9*), congenital lactic acidosis (*X4*, *X22*), maple syrup urine disease (*X15*), glutaric aciduria (*X12*, *X26*), glycogen storage diseases (*X7*), α-ketoadipic aciduria (*X24*), Jamaican vomiting sickness (*X6*, *X29*), dicarboxylic aciduria (*X13*), and 3-hydroxy-3-methylglutaric aciduria (*X8*).

Until recently, organic acid profiling techniques had largely been restricted to urinary or serum constituents but a paper by Goodman and co-workers (*X11*) demonstrates analysis of components of tissue biopsies. They used glass capillary columns for analysis and identified individual components by computer matching of mass spectra against comprehensive files of reference compounds (77 889 entries).

Zlatkis and Kim report a new solvent elution method for the isolation and concentration of volatile metabolites in biological fluids (*X32*) and Stafford et al. (*X27*) report the profiling of volatile metabolites in plasma, urine, breast milk, and amniotic fluid collected from mother–infant pairs. A GC/MS study of volatile organic metabolites in urine from patients with diabetes has been reported by Liebich and Al-Babbili (*X20*). In this study they report increased concentrations of ethanol, propanol, iso- and *n*-butanol, isopentanol, 4-heptanone, and cyclohexanone in this disorder. A subsequent publication describes development of a SIM GC/MS method for quantitative analysis of 4-heptanone (*X21*) using 3-heptanone as internal standard.

Amino Acids and Peptides. Hammond and Savory (*Y3*) have reviewed modern techniques for the detection of amino acids in biological fluids and place particular importance on the use of GC/MS.

A rapid method for analyzing blood amino acids has been described by Mee et al. (*S23*). In the method they apply amino acids (*N*-acetyl methyl ester derivatives) or a derivatized blood extract with appropriate heavy isotope labeled internal standards to a probe and then analyze this by CI mass spectrometry. Unique m/e values were obtained for all amino acids with the exception of leucine and isoleucine which could

not be distinguished by this method. Mass spectral profiles are illustrated from normal controls and patients with maple syrup urine disease, phenylketonuria, and hyperglycinemia which demonstrate the power of this technique.

Various derivatization techniques have been compared by Iwase and Murai (*S17*) in order to determine the preferred one for SIM of amino acids using EI ionization. Based on the fragmentation patterns, they came to the conclusion that *N*-TFA-L-propyl *n*-butyl ester, *N*-benzoyl *n*-butyl ester, *N*-PFB *n*-butyl ester, and *N*-TFA-methyl ester are the preferred derivatives for the concurrent ultramicrodetermination or selective identification of amino acids by SIM. Rangarajan et al. (*Y8*) describe the preparation of amino acid thiohydantoins and their analysis by GC/MS. They suggest these derivatives are particularly useful in protein sequencing.

A method for the SIM analysis of phenylalanine and tyrosine in plasma by preparation of trifluoroacetyl methyl esters has been reported by Zagalak et al. (*Y10*). Deuterium labeled internal standards were used. Deuterated phenylalanine and tyrosine have also been used in kinetic studies of the phenylalanine hydroxylase system (*Y9*). These amino acids were analyzed by MS as their phenylthiohydantoin derivatives after HPLC separation. MacKenzie and Hogge (*Y5*) have made a detailed GC/EIMS study of *NO*-heptafluorobutyryl isobutyl esters of all protein amino acids and report relative intensities of all major fragment ions in tabular form. A published chromatogram illustrates an impressive separation of 18 amino acids using this derivative. As part of a program to detect inborn errors of metabolism, Coffin and Thompson (*Y1*) use *N*-trifluoroacetyl-*N*-butyl ester derivatives of amino acids for their analysis by GC/MS. During this study they found that the disulfide amino acids, cystine and homocystine, form a new species during derivatization, identified by mass spectrometry as a mixed disulfide. Clearly this is valuable information for those quantifying amino acids by GC/MS.

Leimer, Rice, and Gehrke (*Y4*) have published a review containing complete mass spectra of *N*-trifluoroacetyl-*n*-butyl esters of 48 amino acids, and the spectra were discussed in terms of their common fragmentation pathways and factors controlling the formation of fragments. The aliphatic α-amino acid derivatives were generally characterized by a molecular ion, M - 55 (C_4H_7) and M - 101 (butoxyl carbonyl). Hydroxy and sulhydryl amino acids are characterized by loss of the butoxycarbonyl group plus trifluoracetic acid or trifluorothioacetic acid. The dicarboxylic α-amino acids are characterized by predominant M - 101, while the basic amino acids have additional fragments originating from β-cleavage to the ω-amide group.

Nau et al. (*Y6*) describe GC/MS analysis of permethylated peptide containing two to four amino acid residues. Electron impact mass spectrometry was used. A patient suffering from an interesting chronic skin ulceration and edema has been studied by Faull and co-workers (*Y2*). At least 15 dipeptides were identified in the urine by CI mass spectrometry, most of which contained proline or hydroxyproline in the carboxy terminal position. Samples were analyzed from the probe following extensive chromatographic separation. CI GC/MS has also been used in a method recently described for the analysis of urinary and plasma glycine using methane or isobutane as reagent gases (*Y7*).

Schulten and Wittmann-Liebald (*S54*) describe the differentiation of individual amino acids (up to 15) in mixtures by field desorption of phenylthiohydantoin derivatives. The high molecular ion intensities, low fragmentation, and relatively small intermolecular interaction allowed easy discrimination of the individual components.

Sugars and Saccharides. Gas chromatography/mass spectrometry of trisaccharides has been demonstrated by Lundblad et al. (*U23*). These workers studied a patient with deficiency of lysosomal α-mannosidase and found excretion of mannose containing oligosaccharides. They developed a quantitative method for the most common urinary constituent [α-D-mannopyranoside-(1 → 3)-α-D-mannopyranoside-(1 → 4)-2-acetamido-2-deoxy-D-glucose]. Urinary trisaccharides are converted to alditols and methylated prior to being separated by SE-30 capillary columns. A similar method has been used by the same group for identification of a urinary tetrasaccharide (*U22*).

Coduti and Bush have published mass spectral information of *n*-acetyl amino sugar derivatives and disaccharides (*Z1*) and Finne et al. (*Z4*) report GC/MS analysis of TMS ethers of hexosamintol-containing disaccharide alditols obtained from rat brain glycoproteins and gangliosides.

Cataract formation in man involves the accumulation of one of several polyols (e.g., myo-inositol, glucitol) within the tissue of the eye lens and a GC/MS method has been established for studying free polyols and aldoses in this tissue (*Z5*).

As mentioned in a previous section (see Clinical Chemistry), high accuracy (definitive) values for serum glucose are being obtained by isotope dilution mass spectrometry by spiking with labeled glucose (D-glucose-U-^{13}C) and isolating the material as a pure derivative (*W18*). The enriched glucose in serum is converted into 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose which is isolated by sublimation and analyzed by direct probe CIMS.

New glucose production has been measured in 54 infants and children for the first time by continuous three- to four-hour infusions of 6,6-dideuterioglucose tracer (*Z2, Z3*). The use of SIM GC/MS allowed deuterium enrichment in blood glucose to be measured on microliter samples with an error of less than 2%. The enriched plasma glucose was analyzed as an acetate boronate derivative (*Z6*) and the ions of nominal mass 297 and 299 representing the labeled and unlabeled $[M - C_4H_9]^+$ fragments were monitored. This elegant study illustrates the value of the use of stable isotope tracers in metabolic studies, particularly in infants and children, where for ethical reasons use of radioactive tracers cannot be justified.

Steroids, Sterols, Bile Acids and C_{27} Secosterols. With respect to clinical investigation, Adlercreutz has reviewed experiences of his laboratory with quantitative mass spectrometry of endogenous and exogenous steroids in metabolic studies in man (*AA1*). Endogenous estrogens were quantified in urine and bile of pregnant and nonpregnant subjects. Metabolic studies were also carried out with megestrol acetate, estriol, and 16α-hydroxestrone following oral administration.

The Stockholm group of Professor Sjövall has again reported new technology of particular significance to those interested in multicomponent analysis of steroids in body fluids. They have developed ion-exchange derivatives of Sephadex LH-20 (e.g., DEAP LH-20) which are suitable for the resolution of neutral (free) steroids from steroid acids, glucuronides, monosulfates and disulfates (*AA41*) and report the use of these gels in association with computerized GC/MS. Although time-consuming, this technique has great value if a single conjugate type is of importance in a particular situation or disorder. An example is placental sulfatase deficiency which is most easily diagnosed by measurement of maternal urinary 3β-hydroxy-5-ene steroids which are excreted almost exclusively as sulfates. Several patients with this disorder have been studied using DEAP-LH-20 ion-exchange chromatography (*AA49*). Axelson and Sjövall (*AA5*) have also described a selective liquid chromatographic isolation procedure for GC/MS analysis of 3-ketosteroids using DEAP LH-20 for purification of the steroid extracts and Lipidex 5000 (Packard) for purification of TMS ethers prepared using the involatile imidazole reagent. Chromatographic profiling of steroids in urine has been useful for diagnostic purposes and for obtaining new information about the steroid catabolic reactions that take place in healthy and diseased states. A study of urinary steroid excretion in immediate neonatal life of patients with the 21-hydroxylase deficiency syndrome has been published (*AA42*) and GC/MS was used for diagnosis of urinary steroids from a patient with 18-oxidation defect in aldosterone synthesis (*AA43*). Gas chromatography/mass spectrometry has been used for analysis of urinary steroids excreted by patients with virilizing adrenal tumors (*AA9, AA17*) and in study of steroids in plasma (*AA6*) and urine (*AA8*) during human pregnancy.

SIM seems to be well accepted as a method for quantitative analysis of plasma and urinary steroids. Two methods for serum testosterone measurement have been reported, both using radioactive testosterone (^{3}H or ^{14}C) as internal standards (*AA12, AA51*). Martin and co-workers report a SIM method for the determination of conjugated neutral 17-ketosteroids in peripheral and portal venous blood (*AA33*) and a method for the quantitation of the important deoxycorticosterone (DOC) metabolite 3α,21-dihydroxy-5β-pregnan-20-one has been described (*AA40*).

A method for the SIM quantitation of urinary tetrahydroaldosterone by GC/EIMS has been reported (*AA25*) where an analogue, 3β-*allo*-tetrahydroaldosterone, is used as internal standard. The mass spectrum of the methyl oxime trimethylsilyl ether of tetrahydroaldosterone has prominent molecular ions and M − 31 fragmentation particularly suitable for monitoring. A similar study has been made on 18-hydroxy-tetrahydro-11-dehydrocorticosterone (*AA43*). In anticipation of development of a SIM method for aldosterone quantitation, Gaskell and Brooks have investigated the use of alkaneboronate derivatives (*AA19*). Reaction of alkaneboronic acid displaces the equilibrium of aldosterone in favor of the 18-acetal-20-hemiketal which forms a 20,21-cyclic boronate ester. The EI mass spectrum is complex but has a prominent molecular ion and the CI mass spectrum is extremely simple, consisting principally of the protonated molecular ion.

Further work on high resolution SIM of C_{19} steroids in breast tissue has been reported by Maynard et al. (*AA34*) as part of an investigation in the role of these compounds in breast cancer. Nonlabeled analogues were used as internal standards and analyses were made at 10 000 resolution. Dehydroepiandosterone and androstenediol were analyzed using this procedure.

Soon it should be possible to analyze several steroid glucuronide conjugates from biological fluids without prior enzymatic hydrolysis. Thompson (*AA50*) has studied the gas chromatographic and mass spectrometric properties of permethylated estrogen glucuronides and in a similar study Miazaki et al. (*AA35*) used trimethylsilyl-*n*-propyl ester derivatives. However, the practicality of doing similar work with C_{21} steroids having several functional groups (e.g., cortisol metabolites) remains in question.

An example of the use of stable isotopes in studies of the human metabolism of steroid hormones is given by Baillie et al. (*AA7*). These researchers synthesized 3α-hydroxy-5α-(3β,11,11-$^2H_3$)-pregnan-20-one sulfate and administered it to pregnant women in the last trimester of pregnancy. It was shown that 5α-pregnane-3α,20α,21-triol sulfate later isolated from plasma contained three deuterium atoms and examination of the curves of deuterium excess against time indicated that this triol sulfate derives exclusively from the precursor steroid sulfate. From the results it was not possible to ascertain whether 21-hydroxylation preceded reduction at C-20.

Gas chromatography/mass spectrometry has been extensively used for elucidating the structure and intermediates in the side-chain cleavage of cholesterol to pregnenolone by adrenal preparations (*AA11–AA14*, *AA36*, *AA37*) and in studies of mitochondrial and microsomal hydroxylating systems in rat liver (*AA28*). The sex specificity of hepatic steroid hydroxylating mechanisms in the rat has been the subject of several GC/MS investigations over the years. Eriksson (*AA18*) reports the substrate specificity of female rat 15β-hydroxylase and Gustafsson and Stenberg (*AA22*) have used GC/MS to study the neo-natal programming of hepatic steroid metabolism.

A book on steroid mass spectrometry has recently been published by Zaretskii (*AA53*). He has systematically studied underivatized steroids with a variety of functional groups and has paid particular attention to mass spectrometric characterization of the stereochemistry of individual hydroxyl groups.

Smith et al. (*AA46*) have made elegant studies of the fragmentation of TMS ethers of 20-hydroxy-5α-pregnan-3-ones and 20-hydroxy-4-pregnen-3-ones. The base peak in the mass spectra of these compounds is at *m/e* 117, corresponding to the well-known cleavage α to the trimethylsilyloxy group. Each spectrum, however, contained ions at (M − 44) and (M − 59) which appeared to correspond to ions of CH_3CHO and $CH_3CHO + CH_3$, respectively, with concommitant migration of the TMS group. They synthesized (3-^{18}O), (20-^{18}O) and ($^2H_9$-TMS) analogues and studied the fragmentation patterns by CI (isobutane) and EI and demonstrated the side-chain cleavage and TMS migration.

The complete HR mass spectra of progesterone and 29 stereoisomers and alkyl substituted analogues have been analyzed and compared with the aid of a computer program (*AA23*). It was felt that an automated initial treatment would be of considerable value in the detection and analysis of systematic differences between the potentially very similar spectra of the many isomeric compounds examined.

Characterizing the stereochemistry of steroids with several functional groups has always been a problem in mass spectrometry because only a few of the required stereoisomers have usually been available, and frequently data are reported only on underivatized compounds (*AA23*, *AA26*, *AA53*), even though trimethylsilyl ethers are the commonest form in which steroids are analyzed. However, Grote and Spiteller (*AA20*) have published a comparison of the fragmentation patterns of the trimethylsilyl ethers of the eight androstane-3,16,17β-triols, several of which are frequently found in body fluids. The results of the investigation were disappointing since only relatively small differences in relative intensity of peaks were seen and distinction between isomers was possible only by very careful analysis of the spectra. Quilliam and Westmore (*AA39*) have made detailed studies of the EI fragmentation of *tert*-butyl and isopropyl silyl ethers of steroids and suggest that these derivatives provide very much more useful structural information than the commonly used trimethylsilyl ethers. Most available data on steroids have been obtained by EI ionization which is favored because the complexity of steroid mixtures present in body fluids makes it necessary to obtain more information from the mass spectra than is often obtained by CI. However, a recent publication offers illustrations of the use of CIMS with alternative reagent gas in the recognition of specific sterol functional groups (*AA32*).

Sjövall's group have published a full description of their method for total analysis of urinary bile acids (*AA2*). The bile acid conjugates were first separated by lipophilic anion-exchange chromatography, hydrolyzed, and following derivatization (TMS) were analyzed by computerized GC/EIMS. Hi-Eff 8BP and SE-30 columns were used for the analyses. Thirty bile acids were identified or partially characterized, including one tentatively identified which included an unusual 1-hydroxylated compound. Szczepanik and co-workers at Argonne have made a detailed study of the GC/MS characteristics of 50 bile acids (*AA48*). The techniques used differ considerably from those of the Stockholm group. Methyl ester acetates were the preferred derivatives because of instability of TMS ethers and considerable chemical ionization data have been obtained in anticipation of SIM analysis. This communication contains an impressive table of mass spectral data providing the reader with probable structures of about 130 common fragments obtained from EI spectra of bile acids.

Hofmann and Klein (*AA24*) have reviewed mass spectrometric techniques for characterization of bile acid metabolism in man. Although it is their opinion that quantitation of serum bile acids by inverse isotope dilution mass spectrometry is unlikely to compete successfully with radioimmunoassay, they believe isotope dilution studies can give important information on bile acid pool size. Stable isotopically labeled bile acids offer the advantage of freedom from radiation hazard but, more significantly, a greater proportion of the bile acid pool can be labeled than is possible with radioactive compounds. In connection with this work, Cowen et al. (*AA15*) report the synthesis of 11,12-$^2H_2$- and 11,12-$^3H_2$-labeled chenodeoxycholic and lithocholic acids, and this paper contains CI and EI mass spectrometric data.

Bile acids in rats fed normal and high fat diets have been analyzed by GC/EIMS (*AA3*) and new 6-hydroxylated bile acids have been determined in urine from patients with liver disease (*AA47*).

C-26 hydroxylation of cholesterol is a necessary step in the biosynthesis of bile acids in the rat and the possible heterogeneity of the mitochondrial enzyme has been studied using GC/MS (*AA21*). Levy et al. (*AA31*) report the presence of bile acid precursors in meconium, particularly 7α-hydroxycholesterol, (22*R*)-22-hydroxycholesterol, and 26-hydroxycholesterol. Sidechain hydroxylation of sterols is being studied by a number of workers using GC/MS identification of products. Aringer et al. (*AA4*) report 24-, 25-, 26- and 29-hydroxylation of cholesterol, campesterol, and β-sitosterol. Patients with *cerebrotendinous xanthomatosis* have an impaired capacity to convert cholesterol to bile acids and excrete considerable quantities of C_{27} bile alcohols, three of which have been identified as 5β-cholestane-3α,7α,12α,25-tetrol, (24R)-5β-cholestane-3α,7α,12α,24,25-pentol, and 5β-cholestane-3α,7α,12α,23ξ,25-pentol (*AA27*, *AA30*, *AA45*).

It is now generally accepted that the C_{27} secosteroid, vitamin D_3, and its metabolites should be considered as steroid hormones and consequently mass spectrometric methods are being developed for identification and quantification. De Leenheer and Cruyl report a quantitative method based on SIM for the determination of vitamin D_3 in plasma (*AA16*). The hormone is analyzed as an isotachysteryl heptafluorobutyryl derivative using dihydrotachysteryl heptafluorobutyrate as internal standard and the molecular ions (m/e 580 and 594) are monitored. Similarly, a method for quantification of one of the active metabolites, 25-hydroxy-vitamin D_3 has been published (*AA10*). The technique uses 25-hydroxy vitamin D_3 labeled with three deuteriums in the 26 position as internal standard and the base peak at m/e 131 (134 in trideutero) is monitored. These ions are formed by loss of C-25, -26, and -27 with the trimethylsilyloxy group. Difficulties are experienced both in the methods for 25-hydroxy-vitamin D_3 and vitamin D_3 because of the relative instability of these secosteroids and problems with removal of the large amounts of cholesterol present in serum.

An interesting study has been carried out by Hughes and co-workers on constituents of the plants: *Cestum diurum* and *Solanum malacoxylon*. These plants caused hypercalcemia when digested, and EI mass spectrometric evidence finally demonstrated that the active material was identical to a conjugate of 1,25-dihydroxy vitamin D_3 (*AA29*, *AA52*).

The EI mass spectral fragmentation of underivatized vitamin D_3 and related compounds has also been studied (*AA38*, *AA54*).

Prostaglandins and Related Compounds. There have been exciting new developments in the field of arachidonic acid metabolism. Hamberg et al. (*AB7*) report the GC/MS identification of a new unstable intermediate (half-life at 37 °C = 32 s) in the coversion of the prostaglandin endoperoxide PGG_2 to thromboxane B_2 (8-(1-hydroxy-3-oxopropyl)-9,12*L*-dihydroxy-5,10-heptadecandienoic acid) in platelets. The intermediate (named thromboxane A_2) was trapped by addition of methanol or sodium azide to suspensions of washed human platelets incubated for 30 s with arachidonic acid (*AB5*). The mass spectra demonstrated that the intermediates possessed an oxime ring as in thromboxane B_2 but lacked its hemiacetal hydroxyl group. The importance of thromboxane A_2 is that it is an extremely potent inducer of blood platelet aggregation.

Thromboxane A_2 cannot be quantified at present because of its extreme lability, being converted only to the stable essentially biologically inactive metabolite thromboxane B_2. Sweetman et al. (*AB21*) considered it important to identify a thromboxane metabolite in blood or urine which could give a quantitative indication of total body thrombaxane metabolism. Consequently, they have studied the metabolism of radiolabeled thromboxane B_2 in a primate species and, following extensive fractionation and GC/MS analyses, have identified the major metabolites as dinor-thromboxane B_2. Similar findings have also been reported by Kindahl (*AB14*).

Smith et al. (*AB20*) have studied the mass spectral properties of thromboxane B_2 derivatives (oxime silyl ethers, alkyl boronates) and report the identification of this compound in human aorta and serum by SIM of *tert*-butyl TMSE and *O*-methyloxime trimethylsilyl ether derivatives.

The prostaglandin endoperoxides have been shown to be precursors of another new prostaglandin (Prostacyclin or prostaglandin X). This compound was identified by GC/MS as 9-deoxy-6,9α-epoxy-Δ^5-$PGF_{1\alpha}$(*AB10*). In contrast to thromboxane A_2, it is a potent inhibitor of blood platelet aggregation but mimics its instability since this anti-agreggatory activity was lost within 20 min at 22 °C with the formation of a metabolite 6-keto-$PGF_{1\alpha}$, which has also been recently identified by several workers as a metabolite of arachidonic acid and the prostaglandin endoperoxides (*AB2*, *AB3*, *AB11*, *AB16*, *AB18*). Finally, Pace-Asciak et al. (*AB17*) have identified 6,15-diketo-9,11-dihydroxyprost-13-enoic acid as a major metabolite of 6-keto-$PGF_{1\alpha}$ in rat kidney cortex.

In quantitation of prostaglandins and related compounds, SIM is still frequently the method of choice, principally because new active compounds are continually being identified and semiquantitative methods can be established in a very short period of time compared to radioimmunoassay. A quantitative SIM method has been described for the quantitation of PGA_2 using (3,3,4,4-$^2H_4$-17,18-$^3H_2$) prostaglandin A_2 as internal standard (*AB6*). The lower level of detection was 5 pg/mL plasma and levels found in normal subjects were less than 10 pg/mL, findings which contradict the existence of PGA_2 as a circulating hormone. Stable isotope dilution methods for determination of the major urinary metabolite of $PGF_{1\alpha}$ and $PGF_{2\alpha}$ have been developed by Brash and co-workers (*AB1*). This metabolite has the structure 5α,-7α-dihydroxy-11-ketotetranorprostane-1,16-dioic acid and labeled internal standards (^3H and ^2H) were synthesized. The method has a detection limit of 1 ng/mL Cory et al. (*AB4*) reported a SIM method for $PGF_{2\alpha}$ suitable for use in assaying cerebrospinal fluid. The internal standard used for quantitation was a homologue ω-trinor-16-cyclohexyl $PGF_{2\alpha}$ and $^2H_4$-$PGF_{2\alpha}$ was used only as carrier. The $PGF_{2\alpha}$ levels were found to be <2 μg/mL in most patients, although in some neurological conditions levels >10 ng/mL were recorded. Oates et al. (*AB15*) synthesized D_5-tetranor-PGE_1 for use as an internal standard for measurement of tetranor PGE_1. For analysis by SIM of tetranor PGE_1-Me ester methoxime, bis acetate and its pentadeuterio derivative ions at m/e 305 and 309 were monitored. The first use of alkyl boronates in a quantitative SIM method is reported by Smith et al. (*AB20*) who have a preliminary method for the analysis of $PGF_{2\alpha}$ using ($^2H_4$)-$PGF_{2\alpha}$ as internal standard.

Kelly presented a paper at the Ghent quantitative mass spectrometry conference on the GC/MS of prostaglandins (*AB13*). In this communication, he demonstrated the advantages of using the *tert*-butyl dimethylsilyl derivatives for prostaglandin derivatization, although a combined methyl ester/butyl boronate/*t*BDMS ether was used as derivative for the measurement of 19-hydroxyprostaglandin $F_{2\alpha}$ in human semen. 19-Hydroxylated prostaglandins have also been identified in semen by Jonsson et al. (*AB12*) using GC/MS, but to date the reason for the presence of these compounds in high concentration in this fluid is not known.

Interpretation of high and low resolution EI mass spectral data obtained during analysis of authentic prostaglandins has been reported by Raaijmakers (*AB19*) and Horvath (*AB8*, *AB9*).

Biogenic Amines and Related Compounds. Although there are a great number of biologically active amines (biogenic amines), in recent years analytical interest has been focused on a relatively small number of these compounds, particularly on those amines which act as inhibitors or transmitters of signals in the nervous system. The first part of an admirable review of chromatographic methods for the separation of biogenic amines has been published by Seiler (*AC10*). Although it contains relatively little mass spectrometric data, methods for preliminary purification are dealt with in full. A review has been published on the use of SIM in the study of dopamine metabolism (*AC9*) which describes the analysis of dopamine and its metabolites in human brain tissue, rat brain, and cerebrospinal fluid of both normal and psychotic patients.

Although negative ion mass spectrometry is most suitable in studies of environmental samples containing halogens, appropriate derivatization of biologically interesting compounds can render them suitable for this type of analysis. Markey and co-workers (*AC6*) have investigated the use of this technique in the measurement of biogenic amines as pentafluoropropionate derivatives using a modified Finnigan quadrapole mass spectrometer in CI mode. In measurement of dihydroxyphenylacetic acid (DOPAC) in cerebrospinal fluid. it was judged that negative CI was 30 times more sensitive than positive EI. Melatonin-PFP produced a linear standard curve between 2–500 pg which was 100 times better than achieved by EI or positive CI.

Karoum et al. (*AC4*) describe a method for the quantitation by SIM of metabolites of tyramine, octopamine, dopamine, norepinephrine, and epinephrine in cerebrospinal fluid using deuterated internal standards. The following metabolites were analyzed and results reported: *p*-hydroxyphenylacetic acid *p*-hydroxymandelic acid (PHMA), homovanillic acid (HVA), dihydroxyphenylacetic acid (DOPAC), vanilmandelic acid (VMA), *p*-hydroxyphenylethanol (PHPE), and 3-methoxy-4-hydroxyphenyl glycol (MHPG). The authors suggest that in view of the interrelationships among the precursors of these metabolites in the central nervous system, there is need for simultaneous appraisal of those metabolites in various states of mental illness.

Methods for MHPG analysis have also been reported by Murray et al. (*AC8*) and Takahashi et al. (*AC14*). Baillie and co-workers (*AC1*) report a novel method for analyzing MHPG sulfate whereby the conjugate hydrolysis and derivatization are accomplished in a single step: the sulfate is reacted with trifluoroacetic (TFA) anhydride and ethyl acetate, resulting in quantitative conversion to the MHPG tris-TFA derivative.

Electron impact and field desorption mass spectra of dansyl (prepared with 5-di-*n*-butylaminonaphthalene-1-sulfonyl chloride) derivatives of dopamine (DA) and some of its metabolites have been examined by Lehmann et al. (*AC5*). They propose a stable isotope dilution method for the quantitation of dopamine in urine using trisbansyl derivatives of DA-d_0 and DA-d_4 employing two independent methods. Either the molecular ion group of the bansyl derivatives was scanned with the electric detection system in the EI mode or high resolution FD/MS with photoplate detection was employed. In each case the error was within 5%.

There has been interest in the metabolism of 5-hydroxytryptamine (5-HT) since the discovery that anti-depressant and psychosomimetic drugs affect its turnover. Beck and co-workers (*AC2*) describe a SIM GC/MS method for the analysis of 5-HT and its main metabolite 5-hydroxy-indole-3-acetic acid (5-HIAA) using deuterated standard and pentafluoropropionyl (PFP) derivatives. Swahn et al. (*AC13*) have also published a SIM method for the determination of 5-HIAA, HVA, and 4-hydroxy-3-methoxyphenylethylene glycol/MOPEG in cerebrospinal fluid.

Positive CI mass spectrometry has been used for the assay of *N*-methyl-transferase in rat brain using *s*-adenosyl-methionine of 5-methyltetrahydrofolic acid as methyl donors. The products of the reaction, *N*-methyltryptamine (NMT) or *N*-monoethyltryptamine, were assayed by SIM of the MH^+ ion.

Mass spectrometry has been used to positively identify the tryptophan metabolite kynurenine in rat and human brain (*AC3*). This finding is important since tryptophan does affect brain activity and may be related to schizophrenia. A similar study has been carried out by Smith et al. (*AC12*) who have identified melatonin in human CSF and serum for the first time by GC/MS. Like kynurenine, melatonin is a tryptophan metabolite produced in the pineal gland and it has been suggested that it has an endocrine role, particularly in relation to chronobiology, pituitary function, and cerebral physiology. Middleditch (*AC7*) has examined by GC/MS the aldehyde condensation products of biogenic amines and considers that these derivatives would be suitable for analysis of tryptamines by SIM. Tryptamines have also been the subject of research by Shaw and co-workers who have studied the EI fragmentation patterns of specifically deuterated reference compounds (*AC11*). The following compounds were studied: *N*-acetyl-5-methoxytryptamine (melatonin), *N*-acetyl-5-hydroxytryptamine, *N,N*-dimethyl-5-hydroxytryptamine, and *N,N*-dimethyl-5-methoxytryptamine.

Pharmacology. Frequently, examples of pharmacological applications of new techniques in mass spectrometry precede those in biochemistry, probably because samples are "on the shelf" or drug companies are undertaking or financing the metabolic or mass spectrometric studies. It is well known that GC/MS SIM methods for drug analysis, frequently employing stable labeled internal standards, have predominated over the past few years and will no doubt continue to do so. However, there has been a noticeable increase in the application of other new mass spectrometric techniques for pharmaceutical analysis. In the past two years particular attention has been paid to techniques for the analysis of involatile compounds and unhydrolyzed conjugates (e.g., glucuronides) so these aspects will be the main ones discussed.

Collision-induced dissociation appears to offer potential for obtaining analytical information from complex mixtures of body constituents and drugs which are difficult to analyze by GC/MS (*Q39*). This is particularly true for compounds which cannot be separated by GC because of the volatility restriction. It offers a separation method for use in conjunction with special ionization methods such as FD and, compared to direct mass spectometry, little or no sample preparation is required. Konrat and Cooks (*Q35*) report preliminary data on the utilization of this technique for separation and identification of barbiturates and alkaloids. As far as we know, the technique has not been used to analyze biomolecules in body fluids but an interesting example was given of the identification of caffeine in cola beverage by direct injection of aqueous solution into the source where the water ions act as the ionizing reagent. It would seem that the future of this technique is assured and McLafferty and Bockoff foresee its further development for analysis of even complex mixtures by the combination of GC, mass separation and mass spectrometry.

An alternative separation technique for the analysis of labile compounds without derivatization is combined LC/MS, and the recent marketing of a moving belt interface has produced the first applications of this technique to analytical problems in pharmacology (*AD9*). Until now only model compounds (e.g., trimyristin, corticosterone, mestranol, phenobarbitone, and diphenylhydantoin) have been examined, but the results obtained were promising. Preliminary data on a quantitative method for bethanidine (deuterated standard used) showed that the response was linear in the 0–20 ng range and there was no memory effect.

Clearly, however, these reports have been published on the basis of relatively few data and their contribution to multicomponent drug analysis will not be known for some years.

Conjugation of exogenous and endogenous compounds with glucuronic acid is a dominating metabolic reaction in most mammalian species and analysis of glucuronide conjugates by GC/MS is gaining in importance. Whereas until a few years ago hydrolytic procedures were considered essential for freeing the aglycone, increasingly reports are published on direct analysis of glucuronide conjugates. According to the nature of the linking atom the conjugates are classified as *O*-, *N*-, or *S*-glucuronides and recently *C*-glucuronides of drugs have been described for the first time by Richter et al. (*AD23*). Glucuronide conjugates of the drugs sulfinpyrazone and phenylbutazone were identified by direct probe EI MS and other spectroscopic data, and it was shown that C-1 of the glucuronic acid ligand is directly attached to C-4 of the pyrazolidine ring. Studies of intact glucuronides have necessitated the synthesis of appropriate reference compounds and Fenselau et al. (*AD6*) have reported a method for carrying this out using immobilized glucuronyl transferase. Mass spectral data on the TMS ethers of several drug glucuronides are illustrated.

Glucuronic acid conjugates of cannabinoids are of particular importance since greater than 75% of the human urinary metabolites of Δ^9-tetrahydrocannabinol have been found to be excreted in this form. Lyle et al. (*U24*) synthesized glucuronide conjugates of cannabinol, cannabidiol, Δ^8- and Δ^9-tetrahydrocannabinol and analyzed them by GC/MS using both CI and EI ionization following preparation of trimethylsilyl-methyl ester derivatives. The base peak in most of the EI spectra occurred at m/e 317 corresponding to the sugar acid, but all spectra contained ions of low intensity representing the M^+, M – 15 and M – 58 fragments. CI mass spectra obtained with ammonia as reagent gas gave molecular ion species $[(M + NH_4)^+]$ approximately ten times as intense as those of the M^+ recorded under EI but these do not constitute the base peaks as they do in many other underivatized and derivatized carbohydrates.

Lynn et al. (*AD16*) have studied the metabolism of benzomorphan narcotic analgesic drugs (cyclazocine, ketocyclazocine, volazocine, and pentazocine) in rat liver. Following extraction they methylated the metabolites and analyzed them directly by GC/EIMS and identified a series of glucuronides. Good mass spectra of the intact molecules were obtained containing strong molecular ions (25–70%) and major fragments were obtained due to splitting of the glycosidic linkages. An extensive study of the metabolism during rat liver perfusion of *d*-, *l*- and *dl*-methadone has been carried out by Gerber et al. (*AD12*) but no noted differences in the disposition of stereoisomers were detected. The major pathway of metabolism was by *N*-demethylation although glucuronide conjugates were detected in bile and identified intact by GC/MS. Thompson and Gerber (*AD29*) report the separation of isomeric glucuronides of several compounds (1- and 2-naphthols, 2-, 3-, and 4-hydroxybiphenyls, *m*- and *p*-hydroxyphenylphenylhydantoins) by gas chromatography of permethyl derivatives on OV-17 and SE-30 columns. The EI mass spectra of the isomeric glucuronides proved very similar. Since the FD mass spectra of a wide variety of organic compounds exhibit high molecular ion intensities besides weak or absent fragment ions, FD/MS is well suited to the detection

of compounds without derivatization. However, until very recently, field desorption was considered a qualitative technique only, but publications have now appeared on its quantitative applications. Schulten (*AD25*) has described a method for quantitative FD of the anti-cancer drug cyclophosphamide using a hexadeutero analogue as internal standard. Low resolution measurements gave coefficients of variation between 2 and 4% and demonstrated that quantitation is possible in the microgram and submicrogram range.

Kriemler and Richter (*AD15*) have reported a novel method for the study of highly polar conjugates (principally sulfates) of drugs by EI MS with in-situ methylation. They compared the results using this technique to results obtained by FD-MS. Field desorption has been used to study alkali metal salts of sulfate conjugates but although synthetic conjugates used for reference purposes are characterized by extensive cation attachment $(M + Na)^+$ and cluster ion formation (*AD26*), FD of actual sulfate conjugates isolated from biological material often fails to give reliable and reproducible molecular weight information. Kriemler and Richter therefore considered the use of methyl esters but were faced with the instability of these di-esters due to their extreme activity. These workers thus developed a method whereby trimethylanilinium hydroxide was reacted with the sodium sulfate conjugate to yield a quaternary ammonium salt directly on the probe of the mass spectrometer. Controlled thermal decomposition of the salt resulted in methylated products and dimethylaniline which were analyzed by EI MS. This method was used for the examination of metabolic products of carbamazepine (an anti-epileptic drug) and its success demonstrated to the authors the possibility of using this technique as an alternative to field desorption.

Current experience indicates that the most generally applicable methods for quantitative analysis of drugs and metabolites are based on GC/MS, and for the majority of applications selected-ion-monitoring in EI or CI mode is preferred. Horning et al. (*AD13*) have reviewed the use of this technique in drug quantification discussing the problems of extraction methods, choice of derivatives, and internal standards. The relative advantages of using stable labeled analogues, homologues giving ions of the same m/e value, or compounds which give different m/e values but which possess similar GC and extraction properties have been discussed by Millard (*B22*).

A common argument for use of a stable isotope-labeled standard in SIM of a compound of biological interest is its role as a carrier, which may be thought of as a substance that the absorbing, extracting, or chromatographing system cannot distinguish from the compound of interest. Millard et al. (*AD20*) tested this effect during development of a SIM method for octopamine analysis using ($^2H_3$) octopamine as internal standard. They demonstrated that serial injections of nanogram quantities of octopamine prior to analysis of picogram amounts resulted in improved responses suggesting that the active sites in the gas chromatography column had been saturated. However, when nanogram quantities of the labeled compound were co-injected with picograms of unlabeled compound, the adsorption sites for unlabeled compound are not saturated since the signal from the unlabeled compound is not significantly increased.

Garland et al. (*AD11*) describe a GC/CIMS method for the assay of phenacetin and its *O*-desethyl metabolite, acetaminophen, in human plasma using deuterated standards with assay of the MH^+ ions. This group has also published similar methods for the assay of Lidocaine, amitriptyline, and nortriptyline (*AD10*, AD21).

The local anesthetic bupavacaine frequently used in childbirth has been monitored in human fetal and neonatal blood samples by single-ion-monitoring (*AD3*), and transplacental passage of α-methyldopa has been assessed by SIM GC/EIMS measurement in urine from pregnant women and newborn infants (*AD27*). Freed et al. (*AD8*) have also reported a quantitative method for the analysis of α-methyldopa and applied it to the measurement of concentrations in rat brain.

M. G. Horning et al. compared the concentrations of phenobarbital, phenytoin, primidone, ethosuximide, antipyrine, and caffeine in paired samples of saliva and plasma by GC/MS using CI and ^{13}C labeled internal standards (*AD14*). The use of saliva for drug measurement has the advantage that it is obtained by a non-invasive technique particularly suitable for monitoring drug concentrations in children. Claeys et al. (*AD4*) also report data on the use of saliva in studies on the measurement of imipramine and desipramine in different body fluids using GC/CIMS.

Several reports have appeared on the metabolism of steroid drugs. Braselton et al. (*AD2*) have studied the metabolism of the contraceptive steroid norethindrone (17β-hydroxy-17α-ethynyl-4-estren-3-one) in man using GC/EIMS. They have identified about 20 urinary metabolites including one estrogen (ethynyl estradiol). All the metabolites were altered in the A-ring, and the D-ring including ethynyl side chain was unaffected. Anabolic steroid drugs have been around a long time but there is a paucity of information regarding their metabolism, probably because in many cases they were marketed before strict drug control was enforced. However, there has been a renewed interest in the metabolism of these drugs because of their increasing misuse by athletes attempting to improve performance. Urine samples obtained from athletes attending international events are collected and screened for the presence of anabolic steroid metabolites by radioimmunoassay. Positive results are then confirmed by mass spectrometric identification of the actual drug being used since absolute characterization is required before appropriate action can be taken against the offending athletes. In association with this doping control, the metabolism of these drugs by man and primates has been studied by GC/MS (*AD33*) and methods have been developed for the routine analysis of specific compounds (*AD32*). The most commonly used drugs are 19-nor-steroids and steroids with 17α-methyl or 17α-ethyl side chains (e.g., dianabol or 19-nor-testosterone derivatives). The major metabolic processes included were shown to be 6β-hydroxylation and/or reduction of the steroid A-ring.

Studies continue to be made on isotope effects in pathways of metabolism. Stillwell et al. (*AD28*) have investigated the effect of deuterium labeling and its use to differentiate alternate metabolic pathways of drugs containing *N*-methyl groups. The metabolism of methsuximide and N-C^2H_3-methsuximide was studied in rats and GC/MS was used to identify the urinary metabolites. *N*-Desmethyl and *p*-hydroxyphenyl metabolites were the major metabolites of the unlabeled drug, while *p*-hydroxyphenylmethsuximide was the principal metabolite of the labeled material. The effect of deuterium labeling was also investigated for meperidine, antipyridine, and caffeine.

Paraquat (1,1′-dimethyl-4,4′-dipyridyl cation) is a widely used herbicide which has been responsible for over 200 recorded deaths (principally misadventure and suicide). To develop therapeutic approaches to paraquat poisoning, a reliable index of the severity of intoxication based on plasma measurements was clearly desirable. Draffen et al. (*AD5*) report development and use of SIM method for its analysis in serum using a homologue (1,1′-diethyl-4,4′-dipyridyl dichloride) as internal standard.

There have been several papers on the metabolism of cannabinoids in mammalian liver (*AD7, AD10, AD17, AD18*), on the constituents of cannabis resin (*AD31*), and determination of metabolites in plasma of individuals who have smoked the drug (*AD1, AD24, AD30*). Liver metabolites appear to be hydroxylated in most positions on the rings and side chain, and acids have also been identified.

The susceptibility of breast tissue to cancer has caused interest to center on the presence of extraneous substances in breast fluid, a material which is being continually secreted and reabsorbed during adult life. A most recent example is the analysis of nicotine and its major metabolite, cotinine, in breast fluid using SIM GC/MS with deuterium labeled internal standards (*AD22*). Using this technique it was found that nicotine concentration in the breast fluid of smokers could reach a concentration of about 200 ng/mL, a figure an order of magnitude greater than that found in plasma, indicating concentration by the "resting" breast.

Microbiology. The identification of bacterial organisms is important for a set of problems ranging from the search for life on other planets to controlling and preventing disease. Today, several automated and semi-automated techniques promise to reduce the time required for identification of microorganisms to less than a day and to make the ultimate identification more accurate. These techniques have been discussed in a recent article (*AE4*). The two most widely

studied techniques are combinations of pyrolysis and either gas chromatography (*AE10*) or mass spectrometry. Anhalt and Fenselau (*AE1*) report identification of pathogenic bacteria by direct insertion of lyophilized bacteria into the ion source at 300–350 °C. They studied the mass spectra of five species of gram negative bacteria and, although in many cases the same ions were present, differences in relative intensity were significant and reproducible. Further detailed studies indicated that phospholipids, ubiquinone, and metaquinone were important constituents. Another pyrolysis/MS investigation has demonstrated the possibility of discriminating microorganisms at the subspecies level (*AE3, AE5*) and rapid batch processing of up to 30 samples per hour was shown to be possible with a fully automated pyrolysis mass spectrometer/minicomputer system. In order to improve the differentiation between pyrograms, multivariate computer analysis techniques combined with two-dimensional nonlinear mapping of multidimensional data space have permitted efficient use to be made of characteristic features in pyrolysis mass spectra (*AE2*). The model for this study was composed of 20 strains of Listeria bacteria of two different serotypes. Schulten (*AE9*) describes the utilization of pyrolysis FI and FD/MS in the study of microorganisms, and Weijam (*AE11*) reports the use of pyrolysis/EIMS for the analysis of fungi in relation to fungal taxonomy.

The third and newest technique is called linear programmed thermal degradation mass spectrometry (LPTD/MS). The methodology is based on the supposition that a sample of complex biological material will decompose in an orderly and reproducible manner when heated gradually in absence of air. When bacterial samples are treated this way, they would produce a sequence of characteristic molecular fragments that could be monitored mass spectrometrically to produce temperature-dependent profiles of the masses of the decomposition products. Risby and Yergey (*AE8*) have tested this hypothesis on ten bacterial species using a quadrapole mass spectrometer with CI ionization. The temperature of the sample is raised to 400 °C at 20°/min and mass spectra are acquired continuously. A total of 77 ions from all the organisms studied were found to have intensities significantly greater than background levels. These ions were used as candidate ions and specific ion temperature profiles were produced for each of the organisms. It was found possible to distinguish at least one out of the 770 profiles that would differentiate that bacterial strain from the others. In addition to distinguishing the ten organisms, the specific ion-temperature/time profiles can be used to obtain the normal taxonomic relationships between the organisms. Yergey and Risby argue that the results obtained with their technique are just as reproducible as those obtained by conventional pyrolysis/MS, but that a great deal more information is contained in the pyrograms. Other investigators argue that the slow heating cooks the sample and leads to production of species that would not be there otherwise. Conventional GC/MS studies have also been carried out on bacterial constituents as a method of speciation. Analysis of fatty acids (C_{12}–C_{20}) has enabled three pseudomonas species to be differentiated (*AE7*).

A much more difficult problem is identification of specific microorganisms by direct analysis of infected material without cultivation of the infectious agents. Great problems still exist in establishment of this technique, principally because of the unstandardizable host background. Those interested in these problems should consult a book edited by Mitruka (*AE6*) where the application of GC and MS in microbiology is discussed—with references up to the end of 1975.

Although this discussion has centered on the use of mass spectrometry to speciate microorganisms, the techniques described are obviously applicable to many other studies. Pyrolysis/MS studies have been made on a wide variety of materials including viruses, organic polymers, proteins, and DNA. Yergey et al. (*AE12*) are currently attempting to identify the sources of differences in pyrograms of leukemic lymphocytes, so these techniques could provide a great deal of information about the nature of cancer.

ENVIRONMENTAL ORGANIC ANALYSIS

Alford (*AF1*) has updated the literature through 1975 on environmental applications of mass spectrometry including organic and spark source studies. Freudenthal (*AF31*; 60 references) reviewed the environmental applications of mass spectrometry for the Florence International Conference. Areas of applications included: agricultural products, industrial products, drinking water, surface water, ground water, pollution of the soil, air pollution, industrial and domestic effluents, clean-up efficiency of purification stations, and metabolic studies. A review has been published covering the literature from 1970 to 1976 concerned with the determination of volatile hydrocarbons in the atmosphere, primarily alkanes and lower alkenes and their aromatics as a group of unsaturated hydrocarbons (*AF60*; 125 references).

Examples of the use of low and high resolution mass spectrometry for characterization of air- and water-borne particulates, extracts of water-soluble organics and a DDT metabolite from sewage sludge have been published (*AF90*). In addition, a review of environmental organic geochemistry of aquatic sediments has appeared (*AF80*). This treatment attempts to unify the studies of natural carbon chemistry and pollution carbon chemistry in order to strengthen both fields.

Recognition of the phenomenon of long range aerial transmission of organic micropollutants has been discussed together with a challenge that all of the compounds must be identified if the effects of long range transport of air pollution are to be understood. This includes the chemical and photochemical transformation processes taking place during the transportation from source to deposition site (*AF63*). GC/MS techniques are recognized as clearly the most effective present approach to the specific characterization of such complex mixtures. The effect of certain organics is not, of course, limited to aerial transmission but extends to eventual deposition through rainfall or particulate fallout.

A recent paper concerns the impact of methyl chloroform on stratospheric ozone (*AF68*). This particular threat appears to have arisen because of government regulations on limiting the use of trichloroethylene which led to an increased use of the more photochemically inert solvent, methyl chloroform, as a substitute. This type of consideration emphasizes the necessity for having a knowledge of the whole scope of upper atmosphere chemistry through an ability to determine the total atmospheric profile of all synthetic organic substances.

Basic design considerations of a mass spectrometer beam system for applications in measurement of trace components in the stratosphere have appeared. These include the capability of measuring substances from ozone through the nitrogen and chlorine oxides, sulfur oxides, and carbon oxides (*AF66*). Work on measurement of terminal ions in weak atmospheric pressure plasmas has been applied to the atmospheric pressure ionization of trace impurity analysis in gases such as SF_6, Freons, vinyl chloride, NO, and SO_2 (*AF89*). Using Tenax GC collection cartridges, 21 halogenated hydrocarbons, the carcinogens vinyl chloride and trichloroethylene, and numerous oxygen, sulfur, nitrogen, and silicon compounds were identified in ambient air from various areas of the United States (*AF78*). The use of Poropak Q for qualitative analysis of the gaseous atmosphere produced by combustion of fabrics treated with fire retarding chemicals has been described (*AF88*).

The interference of 1-chloro-2-propanol in the determination of bis(chloromethyl) ether in air has been noted (*AF87*). Analysis of organic emissions from stationary sources has been described (*AF86*), as well as the analysis of volatile organics trapped from manufacturing process areas (*AF67*). Olefins, unsaturated hydrocarbons (*AF48*), and aldehydes (*AF43*) have been identified in urban atmospheres. The advantages of chromatography have been emphasized for the quantitative analysis of organic compounds in airborne particulate matter (*AF15*). Discussions of the use of GC/MS in the analysis of environmental chemicals (*AF29*) and in the development of methods for routine application to environmental monitoring (*AF9*) have been presented.

Development and application of GC/MS techniques within the U.S./E.P.A. has been discussed (*AF69*) and computerized algorithms for the qualitative identification of mass spectral data acquired in trace analyses of environmental samples have emphasized the utility of proper computer-aided analysis (*AF22*). Organic pollutant analysis has been carried out using a combined reverse and Clerc type library search (*E24*). A feature article concerning oil spill characterization and identification problems considers the uses of mass spec-

trometry among other techniques. This discussion is cursory and misleading at best (*AF5*). Unfortunately, such misrepresentations of the role and scope of mass spectral capabilities applied using proper expertise plagues much of the governmental effort in environmentally important pollution issues.

Development of negative ion mass spectrometry for detection and quantitation in pollution studies could well play a very important role in the future, particularly in more complex mixtures (*AF39, AF47*).

Cryogenic concentration and acetylene conversion are used to determine water mass spectrometrically (*AF14*). Reverse osmosis has been developed for isolating organics from drinking water (*AF56*). Several studies of volatiles in drinking water have been presented (*AF19, AF32, AF33, AF55, AF97*). Techniques of sampling, GC/MS, and computer identification of compounds in air and water are being developed for the European Economic Community (*AF105*). Phenols and aromatic acids have been studied in river waters (*AF64*). Several studies have been aimed at characterization of the inorganic components in wastewaters including: treated kraft paper mill wastewaters (*AF53, AF54*), analysis of organic compounds in water to support health effect studies (*AF34*), and analysis of domestic wastewaters (*AF35*).

Phthalate ester plasticizers, the class of materials which has been a perpetual artifact in mass spectrometry for the past 20 years, have finally become a new class of marine pollutants (*AF36*). High resolution gas chromatography combined with specific detection has been applied to organic constituents in water (*AF37*). Similar techniques have been used to study the removal of organics by advanced watewater treatment (*AF67*). Capillary gas chromatography combined with high resolution mass spectrometry has indicated the extreme complexity of the trace organic constituents in municipal wastewater effluents (*AF11*). Capillary gas chromatography/high resolution mass spectrometry and elemental composition chromatography have been used to assess the transformations of particular compound classes through a petroleum refinery wastewater treatment process (*AF10, AF12*). This technique holds promise for surveying the qualitative and semiquantitative nature of organics in water and how they are altered in complex treatment trains (*AF10*).

Gas chromatography/high resolution mass spectrometry is an important technique for the detection and estimation of volatile nitrosamines (*AF20*) and chemical ionization mass spectrometry of *N*-nitrosamines has been reported (*AF30*). Studies of ambient air by capillary GC/MS have identified *N*-nitrosodimethylamine (*AF77, AF79*), while a quantitative determination of mitrosoproline, a precursor to the carcinogen found in fried bacon (*N*-nitrosopyrrolidine), has been made (*AF107*). High resolution selected ion monitoring has been used to confirm the occurrences of aflatoxins in agricultural products and physiological fluids (*AF41*). GC/MS has been used to evaluate the composition of exhaled tobacco smoke (*AF46*). Mass spectrometry has been used to study the stereochemistry of hydrolysis products of two stereoisomeric benzo[a]pyrene 7,8-diol-9,10-epoxides (*AF108*). The mass spectra of synthetic cyclopenta[*a*]phenanthrenes are described and an identification of an in-vitro metabolite of a carcinogen in this series is reported (*AF106*). High resolution mass spectrometry has been used to determine the structures of the major adducts formed by covalent binding of benzo-[*a*]pyrene diol epoxide with DNA in vitro (*AF96*).

Synthetic chlorinated organics are of environmental concern because of their persistence, their tendency toward local distribution, the lack of information about the nature of their metabolism, and, in some cases such as the polychlorinated dibenzofurans and dibenzodioxins, are among the most toxic substances known. Detection and quantitation of the toxic hazard, vinyl chloride monomer, has been reported (*AF2, AF85*). Methyl chloride has been determined in ambient air samples by GC/MS (*AF21*). DDT and *o,p'*-DDT have been detected in alfalfa meal, buttermilk, etc., by GC/MS (*AF42*).

Negative chemical ionization in mass spectrometry has been used to study pentachlorophenol and 2,4,5-trichlorophenoxy acetic acid residues (*AF24, AF25*), and preliminary study of organochlorine compounds in human seminal fluid showed pentachlorophenol and other organochlorine residues in every sample (*AF24*). Positive and negative chemical ionization mass spectra have been used for screening for pesticides and polychlorinated biphenyls. The advantages of mass separation of halogenated materials from biological extracts have been discussed (*AF23*). Pentachlorobenzonitrile has been identified in residues in field crops (*AF4*). Chlorophenols used as fungicides in saw mills were shown to be contaminated with chlorinated phenoxyphenols, chlorinated diphenyl ethers, chlorinated dibenzofurans, and chlorinated dibenzodioxins (*AF62*). Mass spectra of octa- and heptachloronaphthalenes have been reported (*AF18*). Fragmentation and rearrangement processes in the mass spectra of perhalogenoaromatic compounds have been described (*AF52*). Photoformation of polychlorinated biphenyls from chlorinated benzines has been shown to occur (*AF103*), and extracts for organochlorine insecticides and polychlorinated biphenyls from water have been studied by various extraction techniques (*AF72*). Capillary GC/MS has been used for the analysis of polychlorinated biphenyls (*AF57*). Methyl sulfone metabolites of PCB and DDE have been determined in a seal from the Baltic (*AF51*) and phenolic metabolites of PCB and *p,p'*-DDE were isolated from Baltic guillemot and seal (*AF50*). GC/MS has been used in the determination of PCB's and DDT in residues from the western Lake Superior ecosystem (*AF104*). Chlorinated phenols have been shown to form during the analysis of chromatographically pure polychlorocyclic ketones by GC/MS (*AF99*). TMS derivatives of chlorinated phenolics have been shown to be important in the analysis of chlorinated phenols, chlorinated phenoxyphenols, and metabolites of PCB's (*AF92*). Octachloro dibenzo-*p*-dioxin has been determined as an artifact in the GC determination of pentachlorophenol (*AF81*). Irradiation of chlorinated diphenyl ethers has been shown to produce chlorodibenzofurans (*AF73, AF74*). Polychlorodibenzofurans have again been found in commercial PCB's (*AF71*). Separation and identification of isomers of polychlorinated dibenzo-*p*-dioxins has been carried out by GC/MS (*AF13*). Calculation of the theoretical isotopic abundances and optimum ion dwell time for TCDD in a pharmacokinetic study has been reported (*AF84*). Isolation of chlorinated dibenzofurans from polychlorinated biphenyls in rice oil has been reported (*AF7*) and confirmed by high resolution GC/MS in the case of Yusho oil (*AF82*).

The major components of some brominated aromatics used as flame retardants have been studied but no bromo analogues of the dioxins and furans were detected in these products (*AF75*). The flame retardant, pentabromotoluene, has been identified in sewage sludge (*AF65*) and the fate of polybrominated biphenyls in soils has been studied (*AF49*). A method for the quantitative estimation of hexabromobiphenyl in food commodities has been reported (*AF102*).

Chlorophenoxy herbicides have been determined in air by GC/MS selected ion monitoring (*AF28*) and GC single selected ion monitoring has been developed to analyze residues of carbofuran and its metabolites in crops (*AF17*). GC/MS analyses of commercial mixtures of phenylalkanes have been reported (*AF61*). The herbicide paraquat has been determined quantitatively in human plasma by GC/MS (*AF26*). Field desorption mass spectrometry of mycotoxins and mycotoxin mixtures has been applied as a screening technique for foodstuffs (*AF91*). Organophosphorus pesticide residues in food have been studied at the ppb level with open tubular column GC/MS (*AF93, AF94*) and detection of organophosphate pesticides in the blood and urine of field workers has been reported using selected ion monitoring (*AF76*). The chemical ionization mass spectra of 23 organophosphorus pesticides have been reported with isobutane using open tubular GC/MS (*AF95*).

Polycyclic aromatic hydrocarbons (PAH's) are produced as byproducts of incomplete combustion of fossil fuels and may be found throughout the biosphere as trace pollutants; many of these compounds are carcinogenic. Mass spectra of isomeric dibenzopyrenes have been reported (*AF101*). Selected ion monitoring has been used to determine diisopropyl naphthalene and phenyl xylylethane (*AF98*). Studies of diesel exhaust particulates have been carried out by high resolution mass spectrometry, including saturated aliphatic hydrocarbons, oxygenates, and polynuclear aromatics (*AF70*). A study of the effect of aqueous chlorination on the aromatic fraction of diesel fuel has been reported (*AF83*). 1,3,5-Trimethylbenzene was chlorinated after 1 h under these conditions. It has been shown that field desorption mass spectrometry can be used to identify photo products of PAH's

absorbed on carbon (*AF3*). Methane–argon chemical ionization mass spectrometry has been used to differentiate PAH isomers (*AF27, AF59*). Using glass capillary chromatography on samples of recent lake and river sediments, river particulates, and street dust and airborne particulates, PAH's have been separated into individual components. Benzo[*a*]pyrene levels in surface sediments and airborne particulates were measured (*AF38*). Polycyclic aromatic hydrocarbons were found to be present in lower concentrations in a 5200-m Bolivian air particulate sample than in one from Antwerp, Belgium (*AF16*). From studies of PAH's in Recent sediments, it has been postulated that at least in Buzzard's Bay, Mass., they result primarily from anthropogenic combustion of fossil fuels (*AF44, AF45*). Polycyclic aromatic hydrocarbons formed during combustion of coal, wood, and kerosene were identified by capillary column GC/MS and compared to airborne PAH's in high and low coal-consuming areas (*AF58*). An impressive study of the composition of coal-derived fluids by capillary column gas chromatography/mass spectrometry has been reported (*AF6*) and GC/MS was used to study the PAH's in soot (*AF100*). A comparison has been carried out between fluorimetric and selected ion monitoring determination of PAH's in organic particulate matter (*AF8*).

It has been reported that 5β-stanols show promise as chemical tracers of fecal pollution in estuaries (*AF40*).

ORGANIC GEOCHEMISTRY

Over the past 15 years, mass spectrometry and later computerized mass spectrometry (both low and high resolution) and GC/MS have been responsible for providing the present level of knowledge of the detailed structure of the suites of organic substances found to occur in the terrestrial sedimentary environments [see *AG14, AG21, AG44* and the biennial series on "Advances in Organic Geochemistry", the most recent being the 1975 edition (*AG17*)]. These studies applying all aspects of mass spectrometry to the oftentimes extremely complex mixtures of organic substances found in carbonaceous sediments have provided a new understanding of: (i) the origins of "chemical fossils" and (ii) the geochemical processes of both early diagenetic and late maturational stages which have given rise to them from biological compounds. This new appreciation of organic ecochemistry has been made possible mainly by advances in mass spectrometry instrumentation coupled with the routine use of open tubular glass capillary columns and the computerization of GC/MS systems to allow efficient handling of the larger amounts of data resulting from the improved GC and mass spectrometric techniques. Important consequences of this new knowledge have emerged in the area of applied geochemistry; thus, oil exploration techniques now include the use of relative abundances of a wide range of hydrocarbons as "fingerprints", and numerical ratios for recognition of oil source rock relationships and of the number of exploration parameters such as the paleo environment of deposition, the maturation, and migrational history. Similar information is gathered in making an assessment of the extent of environmental oil pollution and of the blow-out hazards of marine drilling operations. The past few years have seen several reassessments of the survival history of biolipids and other biochemical compound types in recent sediments. There is mounting evidence that the field will move into studies aimed at identification of the more functionalized and polar substances which will be more sensitive indicators of the geochemical context.

Blumer has articulated one extreme view of organic compounds in nature by describing the limits of our knowledge (*AG4*); however, the real power of advances in mass spectrometry is not properly considered in this assessment. Eglinton and co-workers have recently discussed the natural background of alkanes in the aquatic environment (*AG9*). Studies of the organic matter of eolian dust and its input to marine sediments have been reported (*AG48, AG51*). The biogeochemistry of Mono Lake, Calif. (*AG42*), highly eutrophic lakes (*AG29, AG36*), the Black Sea (*AG48*), and Recent lacustrine sediments (*AG11, AG12, AG35*) have been investigated for their biolipid compositions. Cutins and cutin acids have been reported as indicators of higher plant contributions to Recent sediments (*AG16, AG18*). Significance in taxonomic value of iso- and anteiso monoenoic fatty acids and branched β-hydroxy acids in *Desulfovibrio desulfuricans* has been reported. *Desulfovibrio* species are omnipresent bacteria in sediments in the marine environment (*AG7, AG8*). Monounsaturated fatty acids have been described from an estuarine sediment (*AG54*) and diagenesis of oleic acid has been investigated in an estuarine sediment (*AG26*). The occurrence and significance of the hydroxy fatty acids in a diatomaceous ooze from Walvis Bay have been reported (*AG6*). Studies of kerogen from Recent algal mats from Baja California have been compared with Eocene sediments such as the Green River Formation (*AG41a*). A detailed study of the diagenesis of the side chain of chlorophyll (phytol) has been derived from a combination of simulation experiments and stereochemical studies of the acyclic isoprenoid hydrocarbons (*AG20 and AG13*, respectively). The action of boron trifluoride methanol on isoprenoid acids has been reported and the formation of component artifacts in sediments upon freeze drying has also been pointed out—presumably a result of clay catalyzed dehydration reactions (*AG52*).

Polycyclic compounds have received considerable attention over the past two years. Diterpenoid compounds and other lipids in deep sea sediments have been elucidated (*AG50*). The occurrence of stanols in various living organisms and the behavior of sterols in contemporary sediments have been reported (*AG40*). Sterol diagenesis in Recent sediments from Buzzards Bay, Mass., has been studied (*AG31*). Sterols have been used as indicators of source material for organic matter in sediments (*AG30*). Sterols in a contemporary lacustrine sediment (*AG25*) and the relationship between lipids from *Fontinalis antipyretica* and underlying sediment have been reported (*AG19*). The latter article discusses the sterols, stanols, and isoprenoid wax esters. The molecular fossil from dinoflagellate blooms has been discovered and the structure elucidated for the so-called "Black Sea sterol" (*AG5*). The analysis of steranes and triterpanes in geolipid extracts has been carried out by automatic classification of mass spectra (*AG55*). Computerized GC/MS analysis of the branched-cyclic alkane fractions of a suite of polluted Recent lacustrine sediments, oil shales, petroleum, and biologically degraded oil seeps has been reported (*AG10*). Pentacyclic triterpanes have been characterized from various depths in the early Toracian in the Paris basin. Stereochemical changes in the side chain of the hopane series are proposed as indicators of the degree of maturation in the sediment (*AG22*). The influence of side chain structure, ring/junction geometry and alkyl substituents on the properties of steranes has been studied for 30 synthetic compounds (*AG30*). This basic information on steranes and triterpanes has been used for source rock crude oil correlations (*AG32, AG45–A47*) and also for evaluation of weathering in petroleum and comparison with its possible source (*AG43*). The origin of polycyclic aromatic hydrocarbons in Recent sediments has been studied (*AG29*). GC/MS analysis of nitrogen heterocycles in coal liquids has been carried out (*AG24*). Nitrogen compounds in petroleum fractions have been studied by GC/MS of naphtha (*AG23*); rare polycyclic aromatic hydrocarbon minerals—curtisite, pendletonite, and idrialite—have been analyzed by mass spectrometry (*AG3*). Azaarenes have been reported recently in sediments (*AG2*). A symposium on mass spectrometry in the study of the composition of fossil fuels was reported in the recent American Society for Mass Spectrometry meeting (*AG1*). Since fulvic acids, humic acids, and kerogen comprise the bulk of organic matter in carbonaceous sediments and are of varying degrees of extractability in organic solvents, work continues on trying to understand their chemical structures. Curie-point pyrolysis in combination with low voltage mass spectrometry has been used to gain information on soil humic acids (*AG39*). Pyrolysis GC, pyrolysis MS, and pyrolysis GC/MS have been used to study melanins and humic acids (*AG28, AG37*). Curie-point pyrolysis has been discussed for application to organic geochemistry (*AG34*). Low temperature ozonolysis of methyl shale kerogen has been reported (*AG53*). Possible origin for insoluble organic debris (kerogen) in sediments has been suggested from insoluble cell wall materials of algae and bacteria (*AG41*). Studies on the geochemical origin of organic sulfur compounds have been reported (*AG33*). The observation of homologous tetrapyrroles in a Black Sea sediment sample has also been reported (*AG15*). The potential of carotenoids as environmental indicators of diagenesis in marine sediments has been reported (*AG56, AG57*). A novel pigment called quincyte from an Eocine sediment has been

partially elucidated (*AG58*).

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