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Mass Spectrometry

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OVERVIEW

The chronicle of achievements involving innovative uses of mass spectrometry in investigations of both molecular structure and function forms an impressive testament to the value of this technique in the fields of chemistry, biology, and medicine. The great utility of mass spectrometry is independent of the atomic and molecular constitution of the substances being analyzed, provided that these substances (whether pure compounds or components of highly complex mixtures) can be transformed into gas-phase positive and negative ions which retain the elemental and structural composition of their neutral parent molecules.

The inherent sensitivity and accompanying specificity of mass spectrometry remain unsurpassed by other physicochemical techniques for the qualitative and quantitative analysis of a wide spectrum of molecular structures. Only radioimmunoassay (RIA) procedures rival mass spectrometry for quantitative applications in those situations where a unique substrate is to be considered to which a favorable antibody exists. In truth, these two ultrasensitive techniques are complementary: for relatively small stable substances, mass spectrometry has the clear advantage in cases where relatively low sample throughput is acceptable, while for unstable and/or larger biological substances, RIA is favored and has high throughput capacity.

The father of the field, J. J. Thomson, clearly stated the salient advantages in 1913 (*A5*): . . . "I have described at some length the application of Positive Rays to chemical analysis; one of the main reasons for writing this book was the hope that it might induce others, and especially chemists, to try this method of analysis. I feel sure there are many problems in Chemistry which could be solved with far greater ease by this than by any other method. The method is surprisingly sensitive—more so even than that of Spectrum Analysis, requires an infinitesimal amount of material and does not require this to be specially purified: . . ." [later (*A6*)] ". . . the rays are registered on the photograph within much less than a millionth of a second after their formation, so that when chemical combination or decomposition is going on in the gas in the tube, the method may disclose the existence of intermediate forms which have only transient existence, as well as that of the final product, and may thus enable us to get a clearer insight into the processes of chemical combination."

With sometimes considerable analogy to the experiences of the Three Princes of Serendip, the practice of mass spectrometry entails creation of ions, separation of ions, and measurement of ions or, if one likes, sample preparation, spectrum determination, and substance identification. While mass spectrometry has been the method par excellence for the study of the qualitative and quantitative composition of volatile and easily derivatized substances in the molecular

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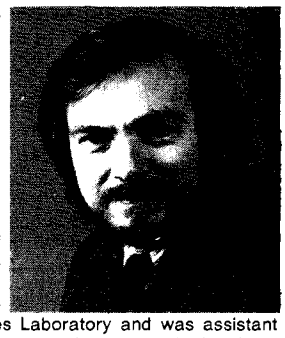
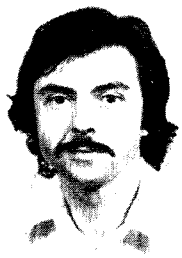


A. L. Burlingame is currently Adjunct Professor of Chemistry and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco; he is also Director of the NIH-supported Bio-organic, Biomedical Mass Spectrometry Research Resources and related intercampus programs at Space Sciences Laboratory and School of Pharmacy, University of California, Berkeley and San Francisco, respectively. 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 in determination of the structure of indole alkaloids. 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. He assumed his current responsibilities in 1978. 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, as director of the mass spectrometry unit, he pioneered 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. His research interests lie in the uses of mass spectrometry in probing the molecular nature of biological function and dysfunction in the context of biomedical, clinical, and environmental research.

Thomas Baillie was educated at Glasgow University where he earned his B.Sc (Hons.) in Chemistry in 1970. He obtained his Ph.D. in 1973, for a thesis on applications of GC/MS in steroid chemistry, under the supervision of Professor C. J. W. Brooks. During the period 1973–1975, he held a Royal Society Fellowship which was spent in Professor Jan Sjövall's laboratory at the Karolinska Institute, Stockholm. During this time, he developed an interest in the application of stable isotope labeling techniques to studies of metabolic pathways, a topic which has remained a central theme of his research activities. In 1975, he took up a staff appointment at the University of London, where he held a lectureship in the Department of Clinical Pharmacology, Royal Postgraduate Medical School, until 1978. Since that time, he has been assistant director of the Biomedical Mass Spectrometry Resource, Space Sciences Laboratory, University of California, Berkeley, and holds an adjunct appointment as assistant professor of pharmaceutical chemistry, University of California, San Francisco. His current interests lie in the application of low and high resolution GC/MS to the analysis of complex mixtures of biological origin, and to the development of stable isotope labeling techniques for use in qualitative, quantitative, and mechanistic aspects of drug metabolism. He is a member of The Chemical Society, The Royal Institute of Chemistry, and the American Society for Mass Spectrometry.



Peter Derrick is a Reader in Physical Chemistry at La Trobe University in Melbourne, Australia. He received his B.Sc. (Chemistry, 1966) and Ph.D. (Physical Chemistry, 1969) from King's College, London. His graduate work, under the supervision of Professor A. J. B. Robertson, was in the classic tradition of chemical physics, giving the first-hand experience and intimate knowledge of instrument "building" which have been invaluable in his subsequent career. His doctoral thesis described a method for determining reaction rates in the picosecond time-frame, which has since come to be known as "field ionization kinetics". He spent some 14 months in the Department of Physics at the Royal Institute of Technology, Stockholm, studying tandem mass spectrometry and photoelectron spectroscopy with Professor Einar Lindholm. During 1971–1972, he worked in the University of California, Berkeley, Mass Spectrometry Group, and he spent three very enjoyable years (1973–1975) at University College, London, with Professor Allan Maccoll. His research interests concern field ionization, fundamental aspects of mass spectrometry and, in recent years, mass spectrometry of macromolecules. During the past four years, he has been "building" an ultrahigh resolution mass spectrometer with a mass range extending to above m/z 20 000. He is a member of the Chemical Society and the Royal Institute of Chemistry, the Royal Australian Chemical Institute, and the American Society for Mass Spectrometry. Peter Derrick is a Ramsay Memorial Fellow (1973), Rennie Medalist (1976) of the Royal Australian Chemical Institute, and Meldola Medalist (1974) of the Royal Institute of Chemistry.

O. S. Chizhov is currently manager of the Laboratory of Physical Methods of Analysis of Organic Compounds and is a professor at the N. D. Zelinksy Institute of Organic Chemistry, Acadamy of Sciences of U.S.S.R., Moscow. He graduated from the University of Moscow in 1958 and received his Ph.D. from the Institute of Chemistry of Natural Products in 1962. His thesis, under the supervision of Professor N. K. Kochetkov, reported elucidation of the structure of a new type of natural lignanes (1,2,3,4-dibenzocyclooctа-1,3-diene derivatives) isolated from seeds of the Far Eastern medicinal plant, *Schizandra chinensis*. Application of various spectroscopic methods in this study was crucial for its success and thus was the starting point for his further interest in developing new instrumental techniques for structural analysis of organic compounds, especially biological macromolecules. He received his D.Sc. from the N. D. Zelinsky Institute in 1967 for his thesis describing his research on employing mass spectrometry in carbohydrate chemistry. In the same year he joined the staff of the N. D. Zelinsky Institute where he became professor in 1974. He is a member of the editorial board of the Russian journal *Bio-organic Chemistry* and regional associate editor of *Organic Mass Spectrometry* from the U.S.S.R.

weight range up to mass 1000, it is only presently that the inventive, concerted thrusts in all of the above operations clearly indicate a quantum breakthrough which holds great promise for the study of biological substances in the mass range of several thousand (*A2*, *A4*). These include field desorption, plasma desorption, laser desorption, and substantial improvements in ion optics and mass range. Developments in other areas such as multichannel array detectors represent technical breakthroughs which will provide sensitivities into the femtogram range (*A3*).

Recent remarks by Dr. Handler (*A1*) clearly summarize the situation in mass spectrometry in the context of the essential need for state-of-the-art instrumentation. "... A remarkable assortment of new techniques, technologies and instruments were developed [since 1967] which can spare not only manpower for other tasks but also enable measurement of phenomena that are otherwise inaccessible. Too few of these new instruments are currently at work to meet urgently sensed needs. They include ... high resolution mass spectrometers ... medium sized computers ... a small number of such instruments will revolutionize the manner of conduct of much of science. ... That style—sharing—extended to the space program and now will be extended to the use of medium priced instruments of chemistry, biology, and physics. But there must first be instruments to share. Science is paced by ideas and instrumentation; it is wasteful and unwise to fail to provide adequate instrumentation if it is our society's intention that our scientific cadre shall be as productive as possible."

Unlike technically less involved fields, it must be recognized that the achievement of a productive symbiosis of state-of-the-art mass spectrometry equipment and highly skilled interdisciplinary expertise still requires a rather long lead time. Continual exposure to new problem areas is vital in order to bring about innovations in mass spectrometry that provide benefits for both routine analysis and research applications in a variety of other fields too numerous to detail.

This review will indicate the general scope of applications of mass spectrometry in selected fields where the technique is utilized extensively. Two major analytical thrusts involving mass spectrometry may be discerned. The first centers on the further development of methodology for the characterization of substances which may be volatilized (following derivatization where necessary) without structural transformation and/or decomposition. The second thrust deals with the pursuit of techniques by which thermally and/or chemically labile substances of extended molecular weight and high polarity may be dealt with. While the rapidly evolving technology of high performance liquid chromatography appears to be ideally suited to the isolation of such species (*C153*), the development of appropriate ionization techniques for characterization of their molecular structure remains one of the most exciting challenges of modern mass spectrometry.

SCOPE

While it is certainly felt that the past decade of reviews from this laboratory indicates to a large extent the scope in changing areas of development and emphasis in mass spectrometry, clearly the most impressive tome of documentation of this period is presented in the First Supplementary Volume of Biochemical Applications of Mass Spectrometry by Waller and Dermer (*C171*). Covering essentially the same decade in 38 chapters, 4 appendices, and approximately 1250 pages, it is an outstanding source treatise with many of the chapters written by authors whose work pioneered the areas of presently extensive application. Topics covered include mass spectrometry instrumentation [Watson (*C175*)], mass spectrometer data acquisition and processing systems [contributions from ten laboratories (*C171*)], metastable ions [Beynon and Caprioli (*C13*)], compound identification by computer matching mass spectra [Heller, McCormick, and Sargent [*E9*], and computer-based identification of unknown [Smith and colleagues (*E7*)]. The section on applications spans 34 chapters, the subjects of which include fatty acids (Odham), lipids (Wood), steroids (Budzikiewicz), bile acids (Elliott), carbohydrates (Radford and DeJongh), terpenoids and carotenoids (Enzell and Wahlberg) amino acids (Vetter), peptide sequencing (Biemann), nucleic acids (Hignite), antibiotics (Borders and Hargreaves), hormones (Brooks and Gaskell), drug metabolism (Bowman and Grostic), and tetrapyrroles (Dougherty). Further topics are respiratory mass spectrometry (Smidt), pesticides [Sphon and Brumley (*AH18*)], alkaloids (Sastry and Madyasta; Hesse), flavor components [Kolor (*AH13*)], pheromones (Stenhagen et al.), stable isotopes (Caprioli and Bier), negative ions [Dillard (*C41*)], toxic residues [Dougherty (*AH4*)], air pollutants [Schuetzle (*AH16*)] and flavanoids (Mabry and Ulubelen). Applications to clinical medicine are discussed by Caprioli et al., separation/identification systems applicable to complex mixtures by McLafferty (*C118*), quantitative mass spectrometry by DeLeenheer and Cruyl, volatiles in biological fluids by Sastry et al., and ^{252}Cf-plasma desorption by Macfarlane (*C104*).

The third indispensable source of distilled information continues to be the Specialist Periodical Report in Mass Spectrometry, Vol. 5 (*B20*), covering the literature from July 1976 to June 1978. It extends from theory and energetics through instrumentation, GC/MS, and applications to drugs, food science, environmental chemistry, organic geochemistry, natural products, organometallic coordination, and inorganic compounds. In addition, there is a highly welcome cumulative index included for the subjects in Volumes 1–5, covering the past 10 years.

The Eighth International Conference on Mass Spectrometry was held in Oslo, Norway, in August 1979 and the proceedings will soon be published (*B32*). The proceedings of the Annual Conferences on Mass Spectrometry and Allied Topics, the 26th of which was held in St. Louis, Mo., and the 27th in Seattle, Wash., are distributed only to delegates and members of the American Society for Mass Spectrometry. The 1980 and 1981 meetings will take place in New York, N.Y., and Minneapolis, Minn., respectively. The Ninth International Meeting on Organic Geochemistry was held at the University of Newcastle-upon-Tyne, England, in September 1979, the proceedings of which are to be published (*B6*). The proceedings of a two-day symposium on mass spectrometry in organic and biological chemistry have appeared (*B30*), as have the proceedings of the Fourth Meeting of the Japanese Society for Medical Mass Spectrometry (*B31*).

Numerous reviews have appeared on specific areas of mass spectrometry. Photoelectron-photoion coincidence has been covered recently by Baer (*G1*) and Eland (*G24*) and photodissociation has been reviewed (*G18*). Multiphoton ionization has been reviewed by Johnson (*H24*) and the broad subject of multiphoton dissociation has been discussed by Lee and colleagues (*H38*) and Beauchamp and colleagues (*H43a*). Reviews on the mass spectrometry of acetylenes (*I14*), the ortho effect (*I18*) and 1,2-hydrogen shifts (*F24*) have appeared. Subjects of further reviews have included field ionization and field desorption (*C9, J30*), field desorption (*J39*), field-induced surface reactions (*J6*), and quantitative field desorption (*J39*). The physics of ion beam collision processes has been covered in some depth in the book edited by Cooks (*L7*), and the determination of gas-phase basicities (*M6*), acidities (*M7*), and electron affinities (*M29*) have all been reviewed recently. The generation of neutral and ionized allenes, cumulenes, and heterocumulenes by electron impact has been discussed by Schwarz and Koppel (*B36*). Selected applications of mass spectrometry have been reviewed by Fenselau (*B7*). Recent books on mass spectrometry have been edited by Middleditch (*B26*) and Merritt and McEwen (*B25*) while Millard has written a text on quantitative mass spectrometry (*B28*). Recommendations for the use of symbols and abbreviations in papers dealing with topics in organic mass spectrometry have been published (*B22*). A book on ion–molecule reactions, edited by J. L. Franklin, has been published in two parts (*B8*) and a review of the use of mass spectrometry in bio-organic chemistry (in Russian) has appeared (*B34*). A compendium on the use of GC/MS in the analysis of essential oil constituents has been published (*B23*).

The *Mass Spectrometry Bulletin* (*B24*), published from Aldermaston, England, continues to provide a comprehensive, but not necessarily timely, coverage of the literature, while *Gas Chromatography–Mass Spectrometry Abstracts* (*B4*) now appears monthly and reflects the rapidly expanding use of GC/MS in a wide variety of disciplines. Three international journals are devoted entirely to mass spectrometry: *Biomedical Mass Spectrometry* (*B2*), *International Journal of Mass Spectrometry and Ion Physics* (*B16*), and *Organic Mass Spectrometry* (*B29*).

Biomedicine. Applications of stable isotopes in this field continue to increase and the proceedings of two international conferences on the subject have been published (*B1, B19*). A selected bibliography of biomedical and environmental applications of stable isotopes over the period 1971–1976 has been compiled by E. R. Klein and P. D. Klein (*B18*); updates of this bibliography are scheduled to appear at two-year intervals, the first of which has been published recently (*B17*). The use of stable isotopes in medicinal chemistry has been reviewed by Halliday and Lockhart (*B14*) and further applications are to be found in the volume by Waller and Dermer (*B39*) in the sections by Caprioli and Bier and by DeLeenheer and Cruyl.

The proceedings of the Italian mass spectrometry meetings held at Riva del Garda in June 1977 (*B9*) and at Rimini in June of the following year (*B10*) have been published, although the proceedings of the 1979 conference in Venice have not yet appeared. This year's meeting will be held in Milan from June 16–18. The Second International Symposium on Quantitative Mass Spectrometry in Life Sciences was held in Ghent, Belgium, in June 1978, and the proceedings were published in the same year (*B5*). A further symposium on the same topic will also take place in Ghent from June 10–13, 1980. A conference on biological oxidation of nitrogen was held in London in 1977 and the proceedings contain several papers relating to the analysis of this class of compounds by mass spectrometry (*B11*). A book entitled "Blood Drugs and Other Analytical Challenges" (*B33*) contains several chapters on application of mass spectrometric techniques. Two additional volumes in the series "Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry" have now appeared, dealing with central nervous system stimulants (*B12*) and analgesics, local anesthetics, and antibiotics (*B13*), respectively. A further volume on cardiovascular, antihypertensive, hypoglycemic, and thyroid related agents is in press. Reviews of the use of mass spectrometry in drug metabolism have been published by Millard (*B27*) and by Bowman and Grostic (*B3*); Self (*B37*) has reviewed the application of MS techniques to the analysis of trace toxic substances in food. A review of quantitative mass spectrometry in biochemistry and medicine has been prepared by Lehmann and Schulten (*B21*). An English translation of the Japanese text on pharmaceutical and medical applications of mass spectrometry has been published (*B38*).

INNOVATIVE TECHNIQUES AND INSTRUMENTATION

In general, the very large and complex suites of all "unknown" substances fall into one of three categories: (1) volatile or volatilizable through chemical derivatization procedures; (2) thermally and/or chemically labile substances which we have not yet learned how to derivatize, especially those of higher mass; and (3) substances presently isolatable which require degradative procedures to generate substances which fall into categories 1 or 2; these degradative procedures

can be highly selective [as in very careful enzymic procedures for carcinogens bound to DNA, for example (*C159*)] or very crude [as in pyrolysis of cells (*C137*) and kerogen]. Obviously the criteria for advances in mass spectrometry are associated with the progression of classes of substances and molecular types from the less tractable categories into the more tractable categories through improved knowledge of handling of particular sample types, especially at low sample levels (≤ micrograms), or through invention of new methodologies to treat these labile materials as such.

The reader is referred to a comprehensive review of trends in instrumentation by McCormick (*C115*) covering two years ending in June 1978.

In this two-year period, the utilization of wall coated open tubular (WCOT) glass capillary gas chromatographic inlets with various mass spectrometers has become established in the United States. Surface deactivation recipes for glass capillary gas chromatography have gone through many stages and have recently been reviewed (*C169*). The previous Grob procedure recommended in our last review, using barium carbonate, gives excellent performance up to a temperature of 220 °C. In the interim, a deactivation procedure using persilylation has permitted extension of the temperature to 350 °C (*C55–C57*). The most recent development has been fused silica columns which have been deactivated by the Grob persilylation procedure with excellent results for steroid TMS ethers (*C141*).

A discussion of optimization of capillary columns regarding the speed of analysis has been presented (*C58*) and comments have been made on glass capillary GC and GC/MS (*C170*), even at subatmospheric outlet pressure (*C36*). A note on diffusion-free pressure regulators for capillary GC has appeared (*C54*) and a more recent assessment of the open split type GC/MS interface (*C65*) now agrees that the glass restrictors are superior to those of platinum. An illustration of the performance which can be obtained from thoughtful combination of the Grob injection techniques, the inert high temperature glass columns, and an all-glass GC/MS open split interface has been shown for a mixture of butter triglycerides up to C-54 by Simon's laboratory (*C145*) using conventional mass spectrometry, and for biomedical (*AG14*) and geochemical samples (*C125*) by Burlingame's laboratory using high resolution mass spectrometry and elemental composition chromatography.

Continuation of work on automated metabolic profiling of organic acids in human urine has been carried out by Sweeley's laboratory using conventional GC and GC/MS where provision is made for quantitation of over 100 components (*C48, C49*). These developments are leading to an interlaboratory intercomparability of GC/MS data sets. A method for the detection of mass peaks using data blocking cross-correlation has been described for computerized GC/MS (*C25*). Hogg has reported promising results using GC/FIMS for hydrocarbon analyses (*C70*). GC/FIMS has been carried out for polynuclear aromatic compounds using the volcano style ion source (*C184*). FD emitters have been used to collect GC fractions for molecular weight determinations (*C85*). GC/photoionization MS has recently been evaluated, using a suite of the relatively low molecular weight organic substances. Mostly molecular ions were observed but with relatively low sensitivity compared to GC/EIMS and CIMS (*C174*).

A rather succinct, well-presented overview of mass spectrometry instrumentation has emphasized the quality of information available with various types of double focusing geometries over those of single focusing and quadrupole mass filters (*C35*). Watson has presented a discussion of instrumentation, including atmospheric pressure ionization, negative ion, secondary ion chromatography–mass spectrometry techniques (*C175*). An updating of selected specialized mass spectrometer data systems may be found in Waller and Dermer, Chapter 3 (*C171*). The polyperfluoropropylene oxide polymers are very useful mass standards from mass 800 to over 5000 (*C173*). These are available commercially under the trade name of Fomblins. Fomblin-L has been discussed by Ligon (*C102*). The quality of mass and relative abundance measurements from a high performance mass spectrometer, the Kratos MS-5074, using a Ferranti-Argus 500 computer has recently been presented (*C84*). Scans were carried out at mass resolutions of 10000 and 40000. The rms of the experimental ppm errors gave a measure of the overall mass measurement accuracy at each resolution. Values of 0.68 and 0.27 ppm were obtained at 10000 and 40000 resolution, respectively, while the corresponding rms of the theoretical errors were 0.62 and 0.23 ppm. The table of the presently accepted exact masses and isotopic abundances for naturally occurring isotopes in the periodic table has recently been compiled (*C172, C178*). A technique based on normal tracer pulse chromatography utilizing stable isotopes and a mass specific detection system has been described for measurement of vapor–liquid or vapor–solid equilibrium (*C134*). A fully automated mass spectrometer with successive introduction of up to 30 samples by means of a direct inlet probe has been described (*C66*). Denne et al. have described a commercially available high sensitivity, high resolution mass spectrometer (Kratos MS-80) which is especially suitable for selected ion monitoring at higher mass resolutions (*C40*). An instrument of comparable performance consisting of a stigmatic, second-order, double focusing mass spectrometer has been discussed and is commercially available as the Hitachi M-80 (*C162*). The performance of a commercial double focusing mass spectrometer and ion kinetic spectrometer, the VG Micromass MM-ZAB-2F, has been described (*C127*) in addition to a system for computer control of its operation (*C19*). Circuitry for solid state magnet control for an A.E.I. MS-902 mass spectrometer has been published (*C177*). A developmental magnetic mass spectrometer incorporating simultaneous ion detection and variable mass dispersion has been used successfully for laser pyrolysis and collision-induced dissociation studies (*C166*). Basic considerations of mass resolution and transmission through a collision cell indicated that post-acceleration after the collision chamber leads to a larger improvement of mass resolution and sensitivity than a similar amount of incident impact energy (*C165*). A simple double focusing mass spectrometer consisting of an electric parallel plate condenser and a double electrostatic quadrupole lens with a small rectangular magnet has been described (*C161*). An instrument for the study of laser-induced photodissociation of ions consists of a tandem quadrupole and permits resolution of ion structure in photodissociation efficiency curves (*C116*). A technique which permits measurement of the dissociation rates of internal energy-related ions has been used to study the isomerization of styrene and cyclo-octatetraene (*C151*).

The superior analytical properties of wall coated open tubular glass capillary columns have minimized the absorptive and catalytic problems for polar compounds, the component chromatographic resolution has increased more than a factor of 10 and the sensitivity in GC/MS has improved considerably owing to the enhanced rate of flow of sample per unit time to the ion source. Nevertheless, compelling problems exist in many fields, for example, biology and environmental chemistry, which are not presently amenable to an attack by gas chromatography. On the separation side for polar, labile, high molecular weight substances, high pressure liquid chromatographic techniques have exploded and are filling this need (*C153*). Of course, development efforts are under way to arrive at suitable marriages between liquid chromatography and mass spectrometry by analogy with GC/MS. Presently the moving band and the direct injection techniques appear most promising for future development (*C3, C118, D40*). A dense gas mass spectrometer interface was proposed as a nozzle–skimmer–collimator system (*C139*). Also, a microliquid chromatograph has been coupled to a mass spectrometer through a jet separator (*C160*). A LC/MS interface using four oxy-hydrogen torches for vaporization of the effluent yielded spectra of arginine and guanosine without severe pyrolysis (*C16*).

While impressive developments of these chromatographic methods for dealing with separation and mass spectral characterization of complex mixtures are progressing with their own particular advantages and disadvantages, the First Prince of Serendip has been particularly busy "combing the waterfront" for what sometimes seems to be magic solutions to many of these problems. The salient concept is to create ions of your sample (whatever it is), use mass analysis to select the components (ions) of interest, and use mass analysis to measure the spectra of the ionic components selected, generated by enhancement of these ions' internal energy in collision, laser-induced (*C103*) or other internal energy enhancement processes.

McLafferty has presented two up-to-date reviews on

MS/MS (*C120, C123*) which are particularly well balanced, with a discussion of the presently feasible advantages and drawbacks and rather cautious projections of the future role. One serious point which tends to be glossed over, minimized, or not mentioned at all in consideration of MS/MS as a competitor for GC/MS (*C31, C50, C182, C183*) or LC/MS is the nature of processes in the *transformation* of the sample into ions, which can then be treated in straightforward ways and certainly improved instrumentally. Put simply, are the ions created representative of the actual molecules in the sample? Has there simply been a physical phase transformation without altering the compositional nature of the original sample? This point is the most serious, of course, in biological and mineral matrices. The point is made most succinctly in a recent communication by Smith, Crain, and McCloskey (*C152*) demonstrating that the MS/MS identification of 1-methyladenine in the pyrolysate of salmon sperm DNA (*C146*) is an artifact of the transformation of sample to ions. In a recent paper, McLafferty's group has shown the advantages in isobaric specificity in using high mass resolution for MS-I of MS/MS, in addition to the sensitivity and mass range improvements inherent in the ability to operate the primary ion beam at 30 kV (*C122*). Also, their discussion of a sector arrangement for a triple analyzer (electrostatic: magnetic:electrostatic) has been discussed in connection with collisional activation in metastable ion decomposition studies (*C119, C121*). The analytical applications of two-dimensional mass spectrometry are presented in a forthcoming chapter by Bente and McLafferty (*C11*).

Unmodified and flame-retardant cellulose have been directly pyrolyzed into a mass spectrometer (*C44*). Glycogen and dextran have been analyzed by Curie-point pyrolysis and field ionization mass spectrometry (*C148*). Quantitative profiling of urine, bile, and fibroblast samples has been carried out by pyrolysis mass spectrometry (*C126*). This latter paper represents an attempt at characterization and classification of otherwise intractable substances and should be considered in detail by those interested in the status of this approach. Normal and malignant human blood cells have been subjected to thermal degradation mass spectrometry (*C181*).

Todd has surveyed the current state of quadrupole mass spectrometry (*C163*). A method for studying the effects of mass discrimination in a quadrupole mass spectrometer has been described (*C180*). A survey and review of chemical ionization instrument technology has been presented which contains 122 references (*C109*). A high pressure chemical ionization source with coaxial electron entrance and ion extraction apertures has been shown to display characteristics of a drift tube allowing determination of ion transport properties (*C75*). Drift tube chemical ionization mass spectrometry has been used to study induced fragmentation in esters (*C138*). Richter and Schwarz have reviewed the more recent work on chemical ionization from the point of view of chemical reactivity and analytical usefulness (*C140*). A paper on the evaluation of ion source conditions for optimal sensitivity of chemical ionization in a Kratos MS-25 has indicated their dependence on the number of atoms in the reagent gas molecule (*C129*). Three thoughtful reviews of negative ions have appeared recently: Jennings (*C77*), Dillard (*C41*), and Bowie (*C20*). Under negative chemical ionization (NCI) conditions, molecules in general exhibit less fragmentation than in positive chemical ionization mass spectra. The sensitivity of the electron attachment process may be very high for compounds containing electronegative elements and the sensitivity may be enhanced for other compounds by making use of fluorinated derivatives. Reagent gases which react as Bronsted bases frequently give $(M - H)^-$ ions in great abundance. The use of selected ion monitoring in NCI leads to subpicogram detection levels in favorable cases.

Perfluorotributylamine has been shown to be useful as a mass marker for the range m/z 19 to 633 (*C45*) and phosphonitrile chlorides in the range m/z 300 to 1000 (*C66*). The negative ions in a hydrogen–nitrogen diffusion flame GC detector fall into two groups: one at m/z 60 and 61 (CO_3^- and HCO_3^-) and the other at m/z 77 (HCO_4^-) (*C113*). The negative chemical ionization mass spectra of dopamine, amphetamine, and Δ^9-tetrahydrocannabinol were detectable in the femtogram range (*C73*) using a quadrupole. Hydroxyl-ion negative chemical ionization mass spectra of 35 steroids have been reported (*C144*), as well as those of oxygenated terpenes (*C23*). Negative chemical ionization GC/MS has been used for routine measurement of melatonin in human plasma at a concentration as low as 1 pg/mL (*C100*). Hydroxide negative ion chemical ionization spectra of cyclic diols has been studied (*C179*). The feasibility of field ionization kinetic studies on negative ions has been demonstrated (*C167*). A discussion of direct mixture analysis by mass-analyzed ion kinetic energy spectrometry using negative chemical ionization has appeared for substituted benzoic acids (*C114*) and hippuric acid (*C88*).

A variety of direct probe experiments has been carried out aimed at developing an ability to run thermally and chemically labile molecules in electron impact and chemical ionization sources. In electron impact, they are referred to as "in-beam" experiments and have been used in connection with determination of the spectra of aliphatic alcohols (*C131*). The quantitative determination of 1,3-bis(2-chloroethyl)-1-nitrosourea under chemical ionization conditions was obtained by direct probe insertion of the mixture residue into a chemical ionization source (*C176*). Direct exposure of solid samples to the reagent gas in chemical ionization has been attempted with Vespel (*C34*), Teflon and glass probes (*C60*). Experimental irreproducibility and inconsistencies among various chemical ionization reports seem to have been eliminated using a metal probe tip coated with a siloxane film as illustrated using taurine, betaine hydrochloride, and sucrose (*C30*). Using a continuous wave CO_2 laser of low intensity $\geq$20 W cm^2, it has been shown that desorption of sugars and tetraalkyl ammonium salts occurs via alkali ion attachment if the organic substance absorbs in the irradiating infrared frequency (*C156*). This is analogous to field desorption of alkali metal salts of these substances. An electron bombardment ion source for a Kratos MS-50 has been modified so that the field desorption emitter can be used as a solid probe (*C42*).

Beynon and Caprioli have presented a detailed discussion of the utilization of metastable ions as an aid in the interpretation of mass spectra (*C13*). The capabilities of "reversed geometry" double focusing mass spectrometers in which the ion beam passes through the magnetic sector before the electric sector have been delineated by Beynon and co-workers (*C14*). Using a variety of the diverse side chains from steroids of a similar tetracyclic carbon skeleton, they have employed the mass selection ability of reverse geometry instruments to determine the structure of a specific portion of a large molecule and permit differentiation of minor structural features in this series of compounds with similar carbon skeletons (*C21*). This is one example of the selective and specific analytical advantages of mass analyzed ion kinetic energy spectra (MIKES). However, these authors are careful to articulate the presence of extraneous peaks in these MIKES spectra as well as to describe the nature of the origin of these extraneous peaks, unrelated to the structure of the species in question (*C6*). In addition, five criteria are suggested in order to establish a distinction between the artifact peaks and the true MIKES peaks. These authors point out "that it may be particularly dangerous to try to characterize a low molecular weight component in a complex mixture by MIKES without knowledge of the high molecular weight components present from which artifact peaks may be expected. It has been suggested (*C87*) that the MIKES method is as powerful for mixture analysis as GC/MS. The results ". . . clearly suggest that this is not necessarily so unless a mass separation stage, such as a quadrupole, that does not depend upon ion momentum is used." Further, Beynon's laboratory has shown that the shapes of MIKES peaks are extremely sensitive to particular instrumental parameters which need to be carefully considered in estimating translational energy releases during fragmentation reaction of ions (*C72*).

General considerations of collision spectroscopy have been discussed in a volume edited by Cooks (*C32*). A discussion of the effect of changes in collision gas pressure on collision-induced fragmentations of benzoyl ions states that more intense fragment ion currents can be obtained at lower pressures than are normally used, and it is suggested that the measurement of appearance energies for fragment ions may be derived from variations of collision gas pressure (*C136*). A method has been described for estimating the distribution of ion lifetimes produced by interacting a fast-moving beam of ions with a collision gas (*C128*). A method for investigating whether a particular reaction is collision-induced or occurs unimolecularly has been described (*C71*). In addition to the

convenience of the MIKES method, the reversed geometry mass spectrometer offers advantages for the study of various charge permutation reactions (*C5*).

The observation of metastable transitions in the first field-free region of a Nier–Johnson double focusing mass spectrometer may be viewed by scanning simultaneously the magnetic field and the electric sector field such that ratio B/E remains constant throughout the scan (*C24*). A high resolution metastable ion spectrum (nominal mass resolution) is obtained in the first field-free region from selected parent mass decompositions. This provides a convenient method for obtaining collision-induced dissociation spectra from selected ions with low internal energy, such as those generated from chemical ionization or field desorption. In this case the collision cell can either be installed in the isolation valve between the source and the electric sector (*C157*) for study of EI- and CI-generated selected ions or the electron impact ion source chamber may be used without modification as a collision cell for selected field desorbed ions of thermally and chemically labile biological substances (*C79, C168*) (vide infra). Broad peaks of non-integral mass in daughter ion spectra can be obtained by linked scans of double focusing mass spectrometers of conventional Nier–Johnson geometry and arise from transitions of higher mass ions in the first field-free region (*C151*). Stereoisomeric androstanediol *tert*-butyldimethylsilyl ethers have been differentiated using linked field scanning (*C47*). B/E linked scanning using a VG Micromass 70/70F was used to probe the potential differences among polycyclic aromatic hydrocarbon isomers (*C150*). A computer procedure for linked scan of a VG 70/70 has been published for both the B/E and B^2/E cases where the daughter ion mass resolution is >500 (*C59*). Using the B/E linked scan, a quantitative assay for 5α-dihydrotestosterone *tert*-butyl-dimethylsilyl ether was developed with a detection limit of ~20 pg in an extract of human blood plasma (*C46*). Other types of linked scans are possible which give rise to constant neutral spectra in mass spectrometry (*C93, C185*). Sequential transitions of metastable ions in double focusing mass spectrometers have been described using toluene and 3-chlorophenol as illustrations (*C91, C92*). Ambiguous assignments from sequential fragmentation processes have also been discussed (*C90*). A DEC PDP-8/I has been described which can be used to acquire metastable transition data on a double focusing Hitachi RMU-7 mass spectrometer (*C74*), as well as an automatic acquisition and evaluation program for metastable peaks occurring in the first field-free region of a Nier–Johnson geometry which is suitable for determination of energy release and energy distribution data (*C106*).

Lehmann and Schulten (*C98*) have reviewed the techniques of mass spectrometry suitable for quantitative analysis in biochemistry and medicine. Baillie has edited a volume on the uses of stable isotopes in both tracer and isotope dilution methods for applications in pharmacology, toxicology, and clinical research (*C7*). The Proceedings of the Third International Conference on Stable Isotopes, edited by the Kleins, has appeared (*C86*). This volume covers stable isotope synthesis, instrumentation, and techniques as well as environmental, biochemical, pharmacological, and clinical applications. An interesting polemic on the uses and functions of deuterated analogues in quantitative mass spectrometry has been published (*C149*). Chiral[^{16}O,^{17}O,^{18}O]phosphate monoesters have been reported in a study of the stereochemical consequences of phosphoryl transfer reactions (*C1*). A program has been written to solve the degree of labeling in deuterated compounds which show an (M – H) peak (*C12*). A method for measurement of ^{18}O kinetic isotope effects for both organic and enzyme catalyzed reactions has been described (*C143*).

Peterson and Hayes have presented a systematic treatment of noise sources within an ion current measurement system. This has been logically developed in terms of expressions which can be used to quantify the relevant noise sources and summarize the results of experimental observations validating this computational approach. They have discussed the significance of the various factors involved in selection of an ion current measurement system (*C135*). In a series of papers, Hayes and co-workers have considered high precision pulse-counting limitations and optimal conditions (*C62*), effective deadtime of pulse-counting detector systems (*C61*), systematic errors in GC/MS isotope ratio measurements (*C112*), isotope ratio monitoring GC/MS (*C111*), and evaluation of the dynamic performance of selected ion monitoring mass spectrometers (*C110*). A careful study of these contributions should begin to reveal the nature and identity of the Third Prince of Serendip.

A pulse counting method for determining the gain of electron multipliers has been described (*C4*). Considerations have been presented on quantitative methodology and detection limits in organic mass spectrometry (*C108*). A discussion of noise generated from the presence of scattered ions and neutrals in mass and ion kinetic energy spectrometers has claimed that, after certain modifications, peaks corresponding to ion arrival rates of 1 s^{-1} may be achieved on a routine basis (*C22*). Performance of a smoothing algorithm for improvement of signal-to-noise ratio in ion kinetic energy data has been published (*C164*). A theoretical discussion of the trade-off of signal-to-noise ratio vs. resolution in Fourier transform ion cyclotron resonance mass spectrometers has appeared (*C107*).

The most obvious methodology for improvement of the overall sensitivity in mass spectrometry from the point of view of minimized amount of sample necessary to record an entire spectrum at a certain signal-to-noise ratio is the development of nonphotographic techniques for the simultaneous detection and monitoring of the entire mass range. The status of such an electrooptical ion detector for use on a Mattauch–Herzog–Robinson geometry has been published (*C18*). Boerboom and co-workers have used a combination of double channel plate, phosphor screen, fiber optic rod, and vidicon camera for simultaneous detection of submicrosecond laser induced desorption processes (*C17*). Hedfjäll and Ryhage have used a similar approach with an LKB 2091 GC/MS operated in the capillary column mode and negative chemical ionization mode (*C63*).

Gries has reviewed quantitative ion implantation from theoretical (*C52*) and practical (*C53*) points of view in connection with the preparation of solid analytical standards. Ion implantation has been used as a method for solid-state standard addition confirmed by the use of the depth profiling capabilities of the ion microprobe for aluminum and silicon in steel and tellurium in gallium arsenide (*C99*). A gas ion probe has been described for analyzing the concentration profiles of gases and solids (*C83*). In addition to the analysis of solids by ion bombardment, the use of a laser probe mass spectrometer received considerable attention (*C89*).

Secondary ion mass spectrometry (SIMS) has begun to show promise in studies of organic substances on surfaces. The reader should consult general references to this extensive subject for further background information (*C10, C64, C68, C101, C117*). Work on SIMS aimed at volatilization of polar compounds has been explored using cationization of organics with transition and noble metal ions (*C51*). Metal chelates of 1,10-phenanthroline with cobalt chloride (*C37*), cesium, palladium, and antimony (*C38*) have been observed using SIMS. The SIMS spectrum of tetramethyl ammonium chloride on platinum shows the intact quaternary ammonium ion (*C39*).

Reviews of field ionization and field desorption techniques have been extensively covered in recent publications by Beckey and Schulten (*C9*), Beckey (*J3*) and Schulten (*J79*). A nanosecond pulsed field desorption time-of-flight mass spectrometer has been used to record spectra of arginine and adenosine (*C130*). The design of a combined FI/FD/EI ion source for use on an A.E.I. MS-9 mass spectrometer has been published which utilizes a micromanipulator for precise emitter alignment (*C69*). Discussion of the application of microfabrication technology to the construction of field emission ionizers has been presented (*C154*). One of these, the volcano, has been used to obtain routine mass profiles for multicomponent samples (*C2*), while another has been incorporated into a magnetic sector instrument with a dual electrostatic quadrupole lens for beam focusing (*C28*). Silicon emitters for field desorption mass spectrometry have been described (*J33, J49*) as well as pretreatment of silicon emitters with tartaric acid dissolved in alcohol for enhancement of ionization efficiency (*C82*). It is claimed that the pretreatment procedure is especially effective for the analysis of peptides containing lysine, arginine, and histidine since it also produces multiply charged ions (*C81*). In an impressive paper from Matsuda's laboratory, polystyrene and polypropylene glycol were shown to give field

desorption mass spectra up to MW 10000 and their suggested use as mass references (*J50*) could be utilized to open a complementary mass scale to that which has been established in EI by the use of Fomblin, the polyperfluoropropylene oxide mixture referred to earlier. As indicated above, combination of field desorption, collision-induced dissociation and B/E linked scanning shows considerable promise for the investigation of underivatized, polar, labile biological substances. Thioether conjugates of acetaminophen (*C8*), suicidal covalent adducts of cytochrome P-450 (*C132*), benzo[*a*]pyrene-bound dinucleotides (*C158*, *C159*), the linkage isomers of disaccharides (*C78*, *C79*), phaeophytin *a* (*C75*), and quaternary ammonium ions (*C43*) have been structurally investigated. Burlingame's group has described field desorption/collision-induced dissociation linked scanning mass spectrometry using a modified Kratos MS-902 (*C26*) and modified Xerox Sigma 7/LOGOS-II capability to permit data acquisition, real-time nominal mass assignment, and field desorption spectrum display concurrently with other on-line operations (*C80*). There are now a significant number of reports in the literature indicating that standard instrumentation, such as an MS-9 or an MS-50, is the limiting factor in the study of high mass, labile materials by field desorption mass spectrometry due to prohibitive loss of sensitivity even at 4-kV accelerating voltage. The reader should consult the FD section of this review for work on MS-50 with the high field magnet, as well as papers on polyester oligomers (*C133*), fluorinated bis(triazenes) at MW 2442 (*C33*) oxo-bis(3,4-toluene-dithiolato)-technetate and related compounds covering the mass range up to 1344 (*C29*). The usable mass range for FD/CID is approximately m/z 1800 for the standard MS-902 (*C80*). The use of a time-averaging computer for accurate mass measurement for high resolution field desorption mass spectrometry has been described (*J65*). Polar nonvolatile organic molecules have been successfully analyzed with a laser-induced desorption technique (*C137*). An impressive spectrum of digitonin, at MW 1228, was demonstrated. Further work on quaternary ammonium salts using fission-fragment and laser-induced desorption has been described; the principal fragmentation pathways are the same (*C147*). A low-intensity CW infrared laser has been successfully applied to multiphoton dissociation of ions derived from diethyl ether (*H8*). At least one class of metal chelates, representative porphyrins, can exchange the central metal for a metal ion coated as a salt on the emitter surface (*C27*). A discussion on the formation of cluster ions and molecular ions in the field desorption of salts has recently appeared (*C142*). Work has continued on electrohydrodynamic ionization mass spectrometry with studies of biochemical materials (*C155*), pyrimidines, purines, nucleosides, and nucleotides (*C94*), and sulfonates (*C95*).

A modification of a double focusing instrument with the introduction of an angle resolving slit has been carried out to study the chemistry of highly excited ions (*C96*). Using this equipment, 1-propanol has been studied at various scattering angles (*C97*).

In a chapter by Macfarlane, californium-252 plasma desorption mass spectrometry has been reviewed (*C104*) showing both positive and negative ion results on biological substances as high in molecular weight as β-endorphin (3487 M + sodium ion). More recently, the utility of this method has been demonstrated by the sequence determination of protected tetra-, penta-, hexa- and deca-nucleotides synthesized by the improved phosophotriester method (*C105*, *C124*).

CHROMATOGRAPHIC/MASS SPECTROMETRIC/ON-LINE COMPUTER TECHNIQUES

As in previous issues of the Specialist Periodical Reports on Mass Spectrometry, C. J. W. Brooks and B. S. Middleditch have presented an authoritative and comprehensive review of advances in GC/MS methodology and applications in Volume 5 of the series (*D7*). Their chapter, which cites 766 references to original papers and 57 to books and review articles, remains by far the most thorough treatment available of the extensive literature on GC/MS and is therefore required reading for all those interested in the technique. Fundamental aspects of GC/MS and representative examples of its usage have been described by Brooks and Edmonds (*D5*). A brief review of GC/MS and its applications (particularly in the area of food chemistry) has been published (*D53*) and an article by D. J. Jenden summarizes applications of GC/MS in the field of psychopharmacology (*D35*). Chromatographic and nonchromatographic sample inlet systems for use in quantitative mass spectrometry have been compared in a book by Millard (*D43*), which is the first text to be devoted exclusively to this rapidly growing area of MS usage. A paper by R. M. Smith (*D51*) serves to illustrate the value of GC/MS techniques in forensic science, while E. C. Horning et al. (*D34*) have discussed the design and application of bioanalytical systems based on computerized GC/MS.

Two major trends in the use of GC/MS techniques may be discerned from a review of the literature published over the past two-year period, viz., (i) the rapidly growing utilization of computer and microprocessor/computer instrumental combinations, and (ii) the widespread adoption of glass capillary GC columns for routine GC/MS work, which has been particularly evident in the field of clinical chemistry (see sections *AC–AG*). A notable exception to the latter trend, however, has been the development by Sweeley and co-workers of packed column GC/MS/COM technology for the automated qualitative and quantitative analysis of complex organic mixtures (*D22*). The value, as one criterion of identity, of accurately determined GC retention index data is frequently overlooked in GC/MS work and it is of interest, therefore, to note the great importance attached to this parameter in the above system for library search purposes. Sweeley et al. (*AG6a*) state that, for their system, "The single most important item of information in the library entry for each compound is the GC retention index, because intralaboratory precision for this datum exceeds 0.2% . . . .", although the authors go on to point out that variations between individual batches of column packing may reduce this figure considerably. Retention indices (5% OV-17) for 231 organic acids, as their trimethylsilyl derivatives, are reported in a paper describing the application of this GC/MS/COM technique to the study of organic acids in human urine (*AG7*), while Burlingame and co-workers (*AG14*), who present corresponding values for selected examples on both WCOT (SE-52) and SCOT (OV-101) glass capillary columns, comment on the high reproducibility of retention index data obtained from such capillary GLC columns.

General aspects of the interfacing of chromatography (GLC and LC) and mass spectrometry have been reviewed by W. H. McFadden (*D40*). EI and CI remain the ionization techniques employed in the vast majority of applications of chromatography–mass spectrometry systems, although the advantages of field ionization and atmospheric pressure ionization in this context have been outlined (*D42*, *D33*).

As quantitative applications of GC/MS continue to increase in almost all fields of application, criteria for the selection of suitable internal standards have received considerable attention (*D43*). Controversy still exists over the (widely assumed) "carrier" role of stable-isotope-labeled internal standards, since definitive information on the subject is lacking. Haskins et al. (*D28*) have reported on the existence of such a "carrier" effect in a GC/MS assay for the antidiarrhoeal drug diphenoxylate, and R. Self has commented on the findings of this study (*T49*).

The development of new derivatives for use in GLC and GC/MS continues, although at a somewhat slower pace than in recent years. A "Handbook of Analytical Derivatization Reactions", compiled by D. R. Knapp (*D38*), contains a wealth of information on derivatives of a wide variety of functional groups, together with practical details of their preparation and references to their MS characteristics. A comprehensive two-part review of derivative formation in the quantitative gas chromatographic analysis of pharmaceuticals has been compiled by J. D. Nicholson (*D46*, *D47*), while the strategy for selecting appropriate derivatives in the GC/MS analysis of lipids has been discussed by Brooks et al. (*D6*). Trialkylsilyl ether derivatives (other than trimethylsilyl) are being employed with increasing frequency in GC/MS work and their use has been reviewed by Poole and Zlatkis (*D49*). Formate esters, employed for many years as protecting groups in organic synthesis, have been proposed recently for use in the GC/MS analysis of 17-oxo-steroids (*D48*), while novel cyclized silyl derivatives of β-hydroxyamines (*D27*) would appear to hold promise for the characterization of compounds of this class, as illustrated in a study by GC/MS of the metabolism

of the β-blocking drug, alprenolol (*S33*).

High Resolution Gas Chromatography/High and Low Resolution Mass Spectrometry. Many of the variables involved in the preparation of high efficiency glass capillary columns and their interfacing to the mass spectrometer have now been well defined, as a result of which the transition from packed to capillary column GC/MS has been effected by a large number of laboratories. Modern apolar columns approach "ideal" performance, although the preparation of polar columns with equivalent performance has not yet been realized (*D24*). A procedure for the deactivation of glass capillaries by silylation has allowed columns coated with nonpolar stationary phases to be operated at temperatures of up to 350 °C (*D25*); this represents a significant development in capillary column technology in that compounds with high retention indices (beyond that of n-$C_{50}H_{102}$) are now amenable to analysis by capillary GC/MS. The introduction of flexible fused silica columns (*D9*) is another noteworthy development; such columns are claimed to provide highly reproducible and inert surfaces for coating, in addition to eliminating the fragility associated with glass columns.

Frank, Nicholson, and Bayer have reported on the synthesis of a novel chiral polysiloxane stationary phase, Chirasil-Val, suitable for the direct gas-phase resolution of optical antipodes (*D15*). The low bleed characteristics of this phase render Chirasil-Val suitable for use in GC/MS applications and the use of this approach in the stereochemical analysis of optically active drugs (*D14*), modified amino acids (*D1*) and the catecholamine metabolite, MHPG sulfate (*D2*), has been described.

Either direct connection or "open-split" interfaces are now employed in the great majority of capillary GC/MS systems (*D40*). Absorption of compounds in the MS ion source was noted in a study by Henneberg et al. (*D30*), who also report on the superior characteristics of glass over platinum capillaries as restrictors in the GC/MS interface. The design, implementation, and performance of a high resolution GC/high resolution MS/real-time computer system has been described by Burlingame and co-workers (*D41*); selected examples are presented of the application of this system to the analysis of complex organic mixtures, from which the enormous potential of HRGC/HRMS/COM technology in this area is self-evident.

Liquid Chromatography/Mass Spectrometry (LC/MS). In contrast to the rapid advances in high performance liquid chromatography (HPLC) technology which have been witnessed over the past few years, progress in developing interfaces for on-line LC/MS has been slow. Two recent reviews on LC/MS (*D26*, *D40*) document the practical difficulties and design considerations involved in the development of on-line LC/MS systems. Guiochon and Arpino (*D26*) have discussed the relative merits of on-line vs. off-line LC/MS; the latter approach is gaining popularity in biomedical applications, where HPLC, employed in a preparative sense, is employed as an initial sample "clean-up" procedure prior to direct insertion or GC/MS analysis. De Ridder and Van Hal (*D11*) have described an automated HPLC system for use in conjunction with GC/MS assays of drugs and their metabolites.

At least four instrument manufacturers (Finnigan, Hewlett-Packard, Ribermag, and VG Micromass) now supply LC/MS interfaces of either the continuous moving belt or direct injection (LC solvent as CI reagent gas) type. The low volatility of solvent systems used in reversed phase HPLC has severely limited the use of this popular LC technique in LC/MS applications. Attempts to alleviate the problem have included the use of the "radially compressed solvent system" reported by Waters Associates in conjunction with auxiliary heating of the continuous belt interface (*D31*), and the use of a CO_2 laser to effect volatilization of the LC effluent (*D3*). Takeuchi et al. (*D52*) have evaluated a jet separator for use in the coupling of "micro" LC columns to a mass spectrometer; LC flow rates are in the order of a few μL min^{-1}, the mobile phase serves as reagent gas in the CI source, and reversed phase solvent systems (e.g., 70% acetonitrile in water) may be accommodated. An alternative, and highly promising, approach to reversed phase LC/MS has been described recently by Karger and co-workers (*D37*). This system features the addition of a modified segmented-flow extractor between the LC and MS which effects the extraction of solutes in the column effluent into a volatile organic solvent; the latter is transported into the MS via a moving belt interface. An important aspect of this technique is that mobile phases containing inorganic buffers can be employed.

Despite the numerous problems which still restrict the use of LC/MS, application of the technique to the analysis of a variety of compound classes has been described. These include herbicides (*D17*), natural products (*D16*), polycyclic aromatic hydrocarbons, carbamate pesticides and dinitrophenylhydrazine derivatives (*D12*), polypeptides (*D10*) and drugs (*D17*, *D29*).

Selected Ion Monitoring. This technique is now used extensively, particularly for quantitative applications of mass spectrometry in the life sciences. The situation regarding nomenclature for this and allied methods, discussed in our previous review (*S13*), has not improved significantly over the past two years, although the terms "selected ion monitoring" (SIM) and "selected ion current profile" (SICP) appear to be favored by the majority of workers and we continue to support their usage. It is not uncommon, however, to find the use of several different terms for the technique by the same author, even in the same paper! Despite the already confused situation over nomenclature, new terminology is still being proposed to describe both the technique itself and the data output it generates. Precise terminology is essential if different MS techniques are not to be confused. The computer-based approach (commonly referred to as "mass chromatography") by which the variation with time in intensity of the ion current at a given m/z value is reconstructed from a series of repetitively scanned mass spectra is frequently confused with SIM. One example of this is found in the paper by Breimer et al. (*D4*) entitled "Selected Ion Monitoring of Glycosphingolipid Mixtures". Although the authors claim that this work represents the first example of SIM at an m/z value in excess of 1000, the recording technique actually used is scanning, and the ion current profiles are reconstructed by computer processing of the stored data. It is also regrettable that all journals do not require that description of SIM assay procedures be accompanied by an illustration of the full mass spectrum of the compound-of-interest, or a reference to the spectrum if already published, from which the basis of the assay may be assessed by the reader.

The application of SIM techniques in pharmacology has been reviewed recently by Jenden and Cho (*D36*), while Ghisalberti (*D23*) has summarized the use of SIM GC/MS in studies of drug metabolism. Applications of SIM GC/MS to the analysis of steroid hormones in biological fluids (*D39*) continue to increase, particularly in view of the development of definitive assays for these compounds based on mass spectrometry (see section *AC*).

A novel technique, termed selected metastable peak monitoring, has been described by Gaskell and Millington (*D19*); in this approach, the combined electrostatic analyzer–magnet scan facility of a double focusing mass spectrometer is employed to bring into focus a metastable ion which is characteristic of the compound-of-interest. Applications of this highly selective technique to the GC/MS analysis of 5α-dihydrotestosterone in human plasma (*D20*) and testosterone in hamster prostate (*D18*) have been described, when the limits of detection of (derivatized) standard compounds were 20 and 30 pg, respectively.

A number of reports have appeared on the use of SIM GC/MS at high (5000–10 000) mass spectrometric resolution, (*D8*, *D13*, *D21*, *D32*, *D50*, *AF4*); the greatly increased selectivity attainable by this approach frequently offsets the accompanying fall in sensitivity of detection and thus renders the technique applicable to the analysis of highly complex mixtures with a minimum of sample "clean-up".

Bile acids and cholesterol have been analyzed as their dimethylethylsilyl ethers by SIM GC/MS using the computer-controlled intensity matching technique (*D44*). The relative merits of SIM and scanning over a limited mass range in the GC/MS analysis of complex mixtures of biological origin have been investigated by Murphy et al. (*D45*).

MASS SPECTRAL INTERPRETATION AND MANAGEMENT TECHNIQUES

For those readers interested in the scope of the usefulness and the present status of research in this wide diversity of

techniques, it is particularly fortunate that there are three recent authoritative reviews available. In addition to those concerning instrumentation, data acquisition, data conversion and reduction, Chapman's recent monograph (*E3*) contains chapters on library search, pattern recognition, and spectrum interpretation. This information is augmented by Heller, McCormick, and Sargent's chapter (*E9*) on compound identification by computer matching of mass spectra, including a discussion of the nature and extent of present collections and the modes of accessibility of mass spectral libraries. The Stanford group has assembled a particularly helpful chapter on the use of a computer to identify unknown compounds, based on their work on the automation of scientific inference (*E7*). They point out that they have found it most useful to concentrate their program development efforts on those parts of the inference task that are most difficult to perform manually, such as structure generation, determination of complete sets of possible fragmentation processes, etc. They have found it more successful to utilize empirical mass spectral data in concert with fragmentation rules to rank structural candidates based on the extent of agreement between predicted and observed spectra, rather than to develop general computational methods for utilizing the mass spectral data to obtain structural inferences in the first place. These methods have certain advantages over other ways of solving chemical structural problems, the obvious ones being completeness and nonredundancy which give the chemist a guarantee that *no alternatives* have been overlooked. These articles are highly recommended reading.

In addition, Mellon (*E16*) have reviewed computerized data acquisition and interpretation with emphasis on the papers at the 24th and 25th Annual Conferences on Mass Spectrometry and Allied Topics, 1976 and 1977. Presently, the volumes from the 26th and 27th conferences are available and are in the possession of the conference participants. A particularly thoughtful assessment of computerization and library search systems has recently been prepared by Henneberg (*E10*). McLafferty and co-workers have discussed the techniques generally available for computer identification of unknown mass spectra by computer retrieval systems which are available to outside users over two international computer networking systems (MSDC/Cyphernet and Cornell/TYMNET) (*E18*, *E19*).

The general problems related to selection, digitization, completion, formatting, and verification of mass spectral reference data in computer-readable format have been outlined (*E2*). A set of procedures has been proposed for construction of a mass spectrum dictionary for the purpose of library searching (*E4*). An overall quality index, consisting of seven quality factors, was used in the preparation of a data base of 41 000 mass spectra. The majority of spectra which the program judged to be unsatisfactory arose from having too few peaks in the spectrum (*E24*). Application of a text search system based on Boolean strategy has been applied to identification of mass spectral data (*E8*).

A combined forward-reverse library search routine for binary coded spectra has been described and tested on 25 000 spectra from various libraries (*E13*). Optimum scaling of mass spectra for computer matching has been considered for compensation of instrument intensity distortions and normalization of spectra for purposes of comparison (*E5*). A retrieval system for binary-coded mass spectra has been described for 9600 low resolution mass spectra from the Aldermaston collection (*E26*). These spectra were reduced to 106 preselected binary coded m/z values each. Such data compression would permit operation of this search system on microcomputers. Another study has concerned the influence of coding errors and matching criteria on the performance of a retrieval system for binary coded spectra (*E25*). A further paper by these authors has shown that the information content for 200 selected m/z values is only about 12 bits rather than 50, owing to errors appearing in the binary coded spectra, and hence is an explanation for the poor performance observed for these retrieval systems (*E27*).

A procedure for subtracting of reference spectra from the mass spectra of mixtures has been used with Probability Based Matching (PBM) to improve the identification of minor components of mixtures (*E1*). Further mathematical techniques have been described for the identification of components in mixtures from the mass spectra of a series of related mixtures (*E20*). Factor analysis has been suggested as a procedure for the separation of mass spectra of mixtures (*E12*). A new theory of error for target factor analysis has been useful for identifying components in mixtures (*E14*). The role of pattern recognition in the computer-aided classification of mass spectra has been reviewed (*E15*). Pattern recognition techniques for the determination of constituent compounds and their relative concentrations in samples have been described (*E6*). A criterion for the confidence with which a user can assess results obtained using a learning machine for classification of mass spectra has been presented (*E21*). Procedures for computer-aided interpretation of steroid mass spectra by pattern recognition have been published (*E22*). Software for the input of chemical structures into a computer system and their pictorial or graphical reproduction have been described (*E28*). An algorithm for converting a non-unique connection table to a unique (canonical) name has been described by assigning unique sequence numbers on the basis of topological properties (*E23*). The determination of fragmentation pathways for single functional groups (*E11*) and multifunctional compounds (*E17*) from computer-processed high resolution mass spectral data has been described.

FUNDAMENTALS OF ION CHEMISTRY

The coverage of fundamental aspects of mass spectrometry is organized according to the technique employed.

Unimolecular Rate Theory and Molecular Orbital Calculations. Coverage of unimolecular rate theory is highly selective, being restricted to those papers directly relevant to mass spectrometry. Oref and Rabinovitch (*F23*) have addressed the question of whether highly excited reactive polyatomic molecules behave ergodically (i.e., is internal energy randomized?) and conclude that in systems studied to date energy is randomized on time-scales $>10^{-12}$ s. They also comment on "allegedly mode-specific excitation" in laser experiments, and the failure of such experiments to provide any substantial evidence of nonstatistical unimolecular behavior. A classical trajectory study (*F13*) of the unimolecular decomposition of neutral C_2H_6 does reveal intrinsic non-RRKM behavior in that there are dynamical restrictions to intramolecular energy transfer among C-H motions and between C-C motions and C-H motions. It is, however, pointed out that RRKM theory (and hence QET) is sufficiently flexible to accommodate this behavior, i.e., the basic model may be incorrect but the theory can still be manipulated to give the required rate. Current bond-specific laser experiments and the interpretation of the results in terms of intramolecular vibrational energy transfer are exemplified by work on benzene (*F4*) and cyclopropane (*F12*).

The work by Lorquet and colleagues (*F7*, *F8*) on nonadiabatic intersections holds considerable implication for mass spectrometry, specifically with respect to the significance for appearance energies (see below) and the application of orbital symmetry rules (see below). The question of whether shape is a property of an isolated molecule (*F28*) is undoubtedly relevant to mass spectrometry, although perhaps not yet significant.

The role of angular momentum in chemical reactivity remains a fascinating question (see *N2* and *N59*). Meisels and colleagues (*F22*) have investigated the $(C_4H_8)^{+\cdot}$ system in detail, and have pointed out that angular momentum becomes particularly important when one among several competitive pathways leads to fragments of low reduced mass and low polarisability.

Coverage of molecular orbital calculations of ion energies and geometries is selective because the number of such papers is so large. Attention is drawn to the new semi-empirical method HAM/3, which has given good agreement with experiment for ionization and excitation energies in a very large number of small and large molecules (*F1*, *F11*, *F19*). The computing time is small. The method is now being used to calculate potential energy hypersurfaces [such as (C_2H_4)] (*F18*).

MINDO/3 has been widely used to calculate not only ion structures but also potential energy hypersurfaces (*F15*, *F16*, *F27*, *K13*) (see also *F26*). Methods of calculating open-shell species by MINDO/3 have been discussed by Dewar and Olivella (*F10*). MINDO/3 has been used to study the Norrish type II reaction (photochemical analogy of the McLafferty

rearrangement), by calculating relevant parts of the potential surfaces involved (*F9*). Two pathways are identified: the triplet reaction in a stable biradical intermediate and a singlet reaction involving direct conversion to product. One general conclusion (*F9*) is that attempts to interpret excited state chemistry in terms of ground state concepts are incorrect in principle, since the courses of excited state are not determined solely by energetic and electronic factors but rather by subtle dynamical considerations.

Ab initio calculations have been reported on a large number of ions, among which are $(RCHOH)^+$ (*F6*), $(C_6H_6)^-$ (*F14*), $(C_4H_9)^+$, $(C_6H_7)^+$, and $(C_7H_{11})^+$ (*F16*), $(C_4H_7)^+$ (*F17*) (see also *F5* and *K14*), $(C_2H_3)^+$, $(C_2H_5)^+$ and $(C_3H_7)^+$ (*F20*), $(C_2H_4O)^{+\cdot}$ (*F3*) and $(C_5H_5)^+$ (*F2, F16*). Calculations on $(C_3H_7)^+$ suggest that the reaction to lose H_2 proceeds via a cyclopropyl-type transition state (*F25*).

A quantitative description of the inductive effect as proposed by Ingold and others has now been given (*F21*) and certain ions are included in the examples considered. A far-ranging review of 1,2 hydrogen shifts has been presented (*F24*).

APPEARANCE ENERGIES

That photon impact and energy-resolved electron impact are the techniques for obtaining accurate appearance energies is now conventional wisdom. Certainly accepted values for *heats of formation* continue to be refined, as measurement are made with increasing sensitivity and resolution (*G7, G14, G36, G37, G51, G52, G54, G59, G73*). The accepted heat of formation of the 2-methyl-2-propyl ion has, for example, recently been revised from about 700 kJ mol^{-1} to 678 ± 3 kJ mol^{-1} (*G35, G53*), and this revision holds considerable implication for the proton affinity scale based on equilibrium measurements. On the other hand, the heat of formation of the $(CH_3CO)^+$ ion has been revised upward, in a study using a supersonic expansion (see below) to reduce the sample's rotational temperature (*G75*). The general question of temperature remains somewhat thorny, and relatively few threshold measurements are in fact corrected to give estimated 0 K values. Interestingly, the ionization efficiency curves of allene are very similar at 215 and 295 K (*G66*). Gas-phase equilibrium measurements can, in principle, provide energy values at a defined temperature (*G42*). Proton affinities have, for example, been determined to obtain heats of formation of $(CH_2{=}CHOH)^{+\cdot}$ and related ions (*G76*). The heat of formation of the norbornyl cation determined from equilibrium measurements shows this ion to be unusually stable (*G64*). A mass spectrometric appearance energy has been used to derive the heat of formation of *neutral* norbornadiene (*G72*). Highly vibrationally excited HF molecules have been detected through shifts (up to 2 eV) in the ionization energy (*G27*).

That obtaining *activation energies for ionic decompositions* from appearance energies is much less straightforward has been clearly demonstrated by recent measurements with photon and energy-resolved electron mass spectrometers (*G33, G34, G44, G71*), where the observed appearance energies indicate that rearrangement can occur at their thermochemical limits (i.e., the rearrangements exhibit no reverse activation energies). Yet, in certain cases (*G44, G71*), the metastable peaks for formally the same reactions clearly show that there are substantial reverse activation energies. The probable solution to this apparent paradox is that there exist minimum energy pathways from reactants to products which are detected in the sophisticated appearance energy measurements, but which do not contribute significantly to the overall decomposition on the time-scale (<10 μs) of the metastable ions (see also *F9*).

One of the several consequences of such situations is that the frequently voiced objections to appearance energies determined with commercial mass spectrometers using semi-log and other techniques are lessened in those cases where the appearance energies are used to estimate activation energies (as distinct from heats of formation) (see below). The effectiveness in mechanistic arguments of activation energies based on semi-log plots is amply demonstrated by Kuck's and Grutzmacher's work on hydrogen and skeletal rearrangements of aromatic hydrocarbons decomposing to $(C_7H_7)^+$ and $(C_7H_8)^{+\cdot}$ (*G40, G41*). Moreover, Baldwin (*G4*) has shown, with measurements of $(C_6H_4)^{+\cdot}$ from benzonitrile, that the semi-log plot method applied to metastable ions on a sensitive mass spectrometer can also give accurate appearance energies and lead to reliable heats of formation.

The broad question of low-energy by complicated reaction pathways has been discussed by Lorquet (*G43*), with particular reference to the role of conical intersections of the potential energy hypersurfaces of different electronic states in setting up such pathways. In the case of $(H_2CO)^{+\cdot}$, it is anticipated that there exist two pathways, a low energy adiabatic "detour" and a higher energy non-adiabatic direct route. The outcome of the competition between these pathways will depend on the amount of internal energy present (*G31, G78*). Tunneling is another factor, which, it is proposed (*G44*; see also *G45*), will introduce a low energy pathway coexisting with a higher energy classical route, in reactions where an H transfer or an H_2 elimination are rate-determining.

Photoelectron–photoion coincidence continues to flourish as a method of studying reactions of ions in selected internal energy states and has been reviewed recently by Baer (*G1*) and Eland (*G24*). In the review period, threshold electron studies, which use a continuum light source, have predominated over the other types of measurement using a resonance lamp at fixed wavelength. A new fixed wavelength instrument designed for study of translational energy distributions has, however, been reported (*G62*; see also *G25*). An important innovation has been the use of synchrotron radiation as a light source for threshold electron coincidence studies (*G2, G28, G30*). Angular distributions of ions with respect to the departing electrons' direction have been measured, and the possibility of non-isotropic distributions has been discussed (*G23*). A non-isotropic distribution could invalidate the usual time-of-flight analysis by which translational energy distributions are obtained. Threshold electrons are produced in auto-ionization processes forming *vibrationally excited* ions (*G47*). It has been suggested (*G47*) that this is a general phenomenon, and this would hold considerable significance for the form of energy deposition functions.

Photoelectron–photoion coincidence measurements have been reported on vinyl fluoride (*G16*), benzonitrile (*G26*), styrene and cyclooctatetraene (*G65*), C_2H_2, H_2S, and D_2S (*G22*), CD_3OH (*G55*), allene (*G59*), BF_3 (*G5*), SO_2 (*G79*), acetone (*G61*), CH_4 and CD_4 (*G60*), and $COCl_2$ and COF_2 (*G38*). $(C_6H_6)^{3\cdot}$ ions from diynes decompose via a common precursor (*G3*); however, decomposition of $(C_6H_6)^{+\cdot}$ ions in general remains enigmatic (*G15*). Using a threshold instrument which permits the introduction of a delay (of some μs) between ion extraction and electron detection, the kinetic shift has been measured directly for certain time-spans (*G63, G67*). No kinetic shift was detected for $(CH_4)^{+\cdot} \rightarrow (CH_3)^+ + H\cdot$ (*G67*), and for $(C_6H_5Cl)^{+\cdot} \rightarrow (C_6H_5)^+ + Cl\cdot$ the kinetic shift was 0.4 eV on increasing ion residence time from 0.7 to 8.9 μs (*G63*).

Attention is drawn to the potentially extremely important electron impact coincidence studies (*G9, G32, G68*). There are several techniques. Fast electrons involved in low momentum transfer ionizing collision are measured in coincidence with either the energy analyzed ejected electrons [dipole (*e, 2e*) technique] or the mass selected ions [(*e, e* + ion) technique]. These techniques are providing results comparable to those from photoelectron spectroscopy and photoionization mass spectrometry, with the added advantage of the easy control and continuous range of electron energies. The binary (*e, 2e*) technique uses large angle, large momentum transfer ionizing collisions, and provides information on molecular orbital momentum distributions (*G8, G48*).

Coverage of photodissociation is divided, admittedly somewhat arbitrarily, into large ions (presented here) and ultrahigh energy resolution measurements on smaller ions (presented under "Laser Spectroscopy"). The subject has recently been reviewed (*G18*). The ions are obtained by electron impact and therefore formed in a wide range of energy states. They are often irradiated from arc sources but sometimes with a tunable dye laser. The large ions have generally been studied in an ion cyclotron resonance (ICR) cell (*G29, G46, G49, G77*), but ion beams have been used (*G50*). Orth and Dunbar (*G57*) have measured the product translational energies and angular distributions for $(CH_3Cl)^{+\cdot} \rightarrow (CH_3)^+ + Cl\cdot$. The angular distribution (anisotropy parameter $B > 1.5$) indicates both that the transition is parallel

polarized (providing information on states involved) and that the dissociation occurs before the ion has had time to rotate significantly (*G57*). The $(CH_3)^+$ product has an average translational energy of 0.58 eV, which is substantially less than the maximum amount available (0.85 eV) but much greater than a statistical proportion (*G57*). Photodissociation studies (without velocity and angle measurement) have been reported for substituted benzenes (*G69*) (see also *G17*), $(CH_2{=}CHCH_2Cl)^{+\cdot}$ (*G56*), $(C_7H_7)^+$ (*G49*), halobenzenes (*G21*), $(C_8H_8)^{+\cdot}$ (*G19, G29*), $(C_8H_9)^+$ (*G19*), alkanes (*G6*), $(C_6H_6)^{+\cdot}$ from hexatriene (*G20*), $(C_2H_5Cl)^{+\cdot}$ (*G46*), $(CH_4)^{+\cdot}$ (*G50*) and various cycloalkanes, alkanes, and alkenes (*G77*).

A number of groups have reported photoionization measurements at very high resolution on supersonic molecular beams. The supersonic expansion means that the sample is rotationally (and vibrationally) "cold", and also that cluster species are formed and can be investigated. Taylor and colleagues, using synchrotron radiation, have determined the O–H bond energy (<4.59 eV) in acetic acid (*G12*), studied dimers of CO_2 (*G39*) and hydrogen bonding in ammonia (*G13*), and have observed autoionization and identified Rydberg series in alkenes (*G80*). At Berkeley, proton affinities of hydrogen halides (*G70*) and ammonia (*G10*) have been measured directly, ionization efficiency curves for clusters of ammonia about a proton have been determined (*G10*), and the dimerization of ethylene has been studied (*G11*). Ionization efficiency curves for dimers of CS_2 have been reported (*G74*). These molecular beam studies promise to make significant contributions to the determination of heats of formation of ions [as exemplified above by the case of $(CH_3CO)^+$ (*G75*)].

LASER SPECTROSCOPY

Spectra of gaseous ions have been measured with sufficient resolution for the determination of molecular rotational constants (*H13, H28*). The methods employ ion beams, narrow laser line widths (typically <1 MHz) and, for the very highest resolution, Doppler tuning. As an example of the resolution attainable, Carrington and colleagues (*H16*), using Doppler tuning, have resolved the four components due to spin-rotation and nuclear hyperfine splitting of each rotational level of the $^2\Sigma^+$ ground electronic state of $(CO)^{+\cdot}$. Each of these four peaks is about 100 MHz or *<1 μeV* wide at half-height. This line width is an *order of magnitude smaller than that in a conventional spectroscopic (Doppler limited) absorption experiment.* Moreover, peak widths of less than 10 MHz have been obtained with $(HD)^+$ (*H14, H42*). In these experiments, the ions' translational energy is varied to scan the spectrum (Doppler tuning), and the transitions (electronic excitation) are detected through collision of the ions with an appropriate neutral gas (*H13, H42*). The different electronic states have different cross-sections for particular ion–molecule (charge exchange) reactions, and hence the actual spectra are of ion intensity as a function of translational energy. A rotational component of the $\tilde{A}^2A_1 \rightarrow \tilde{X}^2B_1$ electronic transition in $(H_2O)^{+\cdot}$ has been detected, using the reaction with H_2 and measuring the intensity of the $(H_3)^+$ product (*H15*).

Rotational components of spectra have also been resolved using photodissociation (*H17, H29, H39*) [also called "predissociation photofragment spectroscopy" (*H29, H39*)]. For structure to be found in the photodissociation spectrum, the upper (excited) state must possess a significant potential well, yet must be able to fragment by predissociation. Further, the predissociation must be sufficiently slow to limit line broadening and sufficiently fast for the fragments to be measured mass spectrometrically. The widths of the rotational lines observed with $(O_2)^{+\cdot}$ using Doppler tuning are limited by the natural linewidth (0.008 cm^{-1} in some cases) (*H17*), and the predissociation lifetimes have been determined (*H29*). Again, the resolution obtained in this spectroscopy of ions is far better than the Doppler limit of a conventional spectroscopic experiment. Very high sensitivity has been obtained in a two-photon infrared photodissociation (see below) involving vibrational levels of $(HD)^{+\cdot}$ with population factors of 0.001 (*H14*). Absolute accuracy of measurement is placed at ±0.005 cm^{-1} (i.e., 0.6 μeV) with room for improvement (*H14*). The photodissociation spectrum of $(O_2)^{+\cdot}$ across the whole visible region has been reported at resolution of 3 cm^{-1} (*H30, H31*). A general theoretical treatment of photodissociation has appeared (*H44*).

Multiphoton ionization techniques promise to make very substantial contributions to mass spectrometry in the next few years (*H6, H7, H18, H46*). Multiphoton ionization has been reviewed recently by Johnson (*H24*), and the broad subject of multiphoton dissociation has been reviewed by Lee and colleagues (*H38*). Using molecular beams, fragmentation patterns following multiphoton ionization have been measured as a function of wavelength for benzene (*H46, H47*), butadiene (*H47*), NO (*H47*; see also *H45*) and I_2 (*H47, H48*). 3-Photon and 6-photon processes are involved in the ionization of iodine (*H48*). Using an H_2 laser (7.70-eV energy), two-photon ionization of benzaldehyde leads to formation of $(C_7H_6O)^{+\cdot}$ and $(C_7H_5O)^+$ (*H6*), and the use of a rare gas halide laser for multiphoton ionization has been reported (*H33*). NO_2 and $(C_6H_5)_2CO$ have been studied by the Russian group (*H5*). The selectiveness and versatility of multiphoton ionization as a means of producing ions for mass spectrometry are stressed in a paper demonstrating two-photon ionization of benzene (*H7*). The total ionization is measured as a function of wavelength in a multiphoton study of cyclic alkanes (*H21*). An accurate threshold can be determined for certain multiphoton ionization processes (*H41*).

It has been shown how certain positive ions can be photodissociated using low intensity infrared laser radiation, and the results may come to provide information not only on ion decompositions but also collisional and radiative decay mechanisms (*H8, H43*). Further, the photodissociation spectra contain information on vibrational frequencies of the *lower* state of the dissociated ion, and it may be possible using this sort of approach to, in a sense, mimic infrared absorption spectra. It has also been possible to photodissociate the negative ion $(CH_3OHF)^-$ under collisionless conditions using infrared laser radiation (*H34*). A gas-phase infrared spectrum has actually been measured directly for an ammoniated ammonium ion (*H37*).

Laser-induced electron photodetachment is a well established and powerful technique, providing precise information on negative ions and, in particular, on electron affinities (*H20, H22, H23, H49, H50*). The experiments tend to be referred to as "photoelectron spectroscopy" when using a fixed-frequency laser (electron energy measured) and as "photodetachment spectroscopy" when using a tunable laser (frequency dependence of electron production measured). Very recently, multiphoton electron detachment of the benzyl anion has been reported. At least 7 photons are absorbed, so that the electron detachment is "vibrationally driven" (*H35*). This coupling of vibrational and electronic degrees of freedom violates the Born–Oppenheimer approximation. Using an argon ion laser, photoelectron spectra have been measured for negative ions of iron carbonyls, providing accurate electron affinities and information on vibrational frequencies, electronic states, and Fe–CO bond strengths (*H19*).

Matrix isolation experiments are increasingly concerned with ions and, although it is recognized that the matrix material can perturb the ions' energy levels, the results do provide spectroscopic information on species for which there is otherwise little data. For example, infrared absorption spectra have been reported for $(CF_3)^+$ (*H32*), $(CH_3X)^{+\cdot}$ (*H2*), $(CCl_2)^{+\cdot}$ (*H1*), $(CH_2Cl_2)^{+\cdot}$ and $(CH_2Br_2)^{+\cdot}$ (*H4*) and $(CHClCCl_2)$ (*H3*). In many cases, the ultraviolet absorption spectra are also presented.

Laser-induced fluorescence spectra of ions such as $(C_4H_2)^{+\cdot}$ (*H9*), fluorobenzene molecular ions (*H12*) and $(C_6H_6)^{+\cdot}$ (*H10*) trapped in solid matrixes generally show well-resolved vibrational structure. Interestingly, the laser-induced fluorescence of *s*-trichlorobenzene molecular ions has been measured both *in the gas-phase* and in a matrix, and there is little difference between the spectra (*H27*). This indicates that the matrix is not seriously perturbing the ion. The laser-induced fluorescence spectra of 2,4-hexadiyne (*H26*) and fluorobenzene (*H11*) ions have also been measured in the *gas-phase*.

Emission spectra have been reported for $(N_2O)^{+\cdot}$ in a flowing afterglow experiment (*H40*), and for octatetraene ions in a crossed beam experiment (*H25*). Neutron diffraction has been used to determine the structure of the ion $(H_3O(H_2O)_2)^+$ in a solid crystal; the ion is highly distorted from trigonal symmetry (*H36*).

ELECTRON IMPACT (EI) MASS SPECTRA

Few investigations of fundamental aspects of ion chemistry

rely these days solely on electron impact (EI) mass spectra. The integrated time-window (up to μs) and the ill-defined internal energy tend to preclude making any significant contribution, although there are of course exceptions.

Reviews on the mass spectrometry of acetylenes (*I14*) and on the ortho effect (*I18*) have appeared. Mass spectra of ^{13}C-labeled alkanes have been reported (*I12, I13*). Labeling with ^{18}O has revealed that aryl group migrations occur in phenylbenzoate ions (*I17*). It has been concluded that cyclohexyl rings suffer little conformational excitation during EI (*I16*). Elimination of stable neutrals from cyclohexylamines (*I20*) and cyclohexylacetates (*I19*) have been studied. It has been shown that in 4-*tert*-butylcyclohexyl bromide (or chloride), alkyl radical loss is assisted by backside attack by the halogen (*I10*). A similar sort of mechanism is proposed for decomposition of δ-substituted alkynes (*I1*).

Papers have appeared concerning the retro-Diels-Alder reaction (*I3, I8, I15*); loss of water from ester molecular ions (*I9*), loss of hydroxyl from alkylnitrobenzenes (*I6*), loss of carbene from annulenes (*I4*), aminoethers (*I7*), cyclopropanes (*I2*), and stictane triterpenoids (*I11*).

Negative ion mass spectra, where low energy electrons formed in secondary processes, have been investigated for polychlorinated diphenyl ethers (*I5*).

FIELD IONIZATION AND FIELD DESORPTION

Field ionization (FI) and field desorption (FD) has been one of the most active areas of mass spectrometry during the past two years. Beckey (*J3*) has reviewed field ionization and field desorption (75 refs.), Schulten (*J79*) has reviewed field desorption (302 refs.), Block (*J6*) has reviewed field-induced surface reactions and there has been a review of quantitative field desorption (54 refs.) (*J39*).

There are indications that FD holds exciting promise as a method of forming gaseous macromolecular ions ($m/z > 5000$) from thermally labile and nonvolatile compounds. FD mass spectra, obtained using silicon microneedle emitters (*J49*), have been reported for polystyrene showing *peaks up to* m/z *11 000* (*J50*). Ions of similar masses have been observed using carbon microneedles in FD of polyglycols (*J57*). The latter results were obtained with a new grand-scale double-focusing mass spectrometer, whose design and construction have been described (*J11, J12*) and which has been "built" for the specific purpose of investigating FD of macromolecules. Both in this work (*J57*) and in that in Japan (*J50*), the massive ions were detected using standard electron multipliers operated at standard dynode potentials, i.e., special detection techniques were not required.

Development of emitters, the crucial factor in any FI/FD experiment, continues. Besides the already mentioned silicon microneedles (*J49*), the use of platinum dendrites prepared electrolytically (*J85*) and of tungsten microneedles (*J62*) has been advocated. The advantages of smaller carbon microneedles for FD have been described (*J26*), and a method for very rapid production of emitters has been discovered (*J46*). X-ray crystallography and Auger spectroscopy have been applied to carbon microneedles (*J58*). Both the substrate (WC) and the needles (C) are highly crystalline; the needles are not graphite (*J58*).

Formation of negative ions by FI has been discussed with reference to some earlier experimental results (*J56*). Negative field ions from tetracyanoethylene have been observed and, moreover, their kinetics of decomposition determined by the field ionization kinetics (FIK) technique (*J97*). Precautions taken reduced, but could not eliminate, the electron emission which tends to accompany formation of negative field ions (*J90, J97*). FD of negative ions has been reported as an effective technique for certain compounds (*J90*).

Field ionization kinetics has been a particularly active area of mass spectrometry during the past two years and its application has been extended to negative ions (*J97*), as mentioned, and field desorbed ions (*J99*). An ion source has been constructed which allows measurements to be made at known high temperatures (up to 900 K) (*J9*). From consideration of the fraction of molecular ions decomposing at various temperatures, Brand and Levsen (*J10*) conclude that an average energy of 0.2–0.4 eV is transferred to hexanes and diethylester during the field ionization process. This determination is based on the assumption that the internal energy of the molecular ion can be effectively regarded as the sum of two separate distributions: one energy distribution similar in form to the (thermal) vibrational state population of the neutral precursor and a second energy distribution characteristic of the FI process. The extent to which this assumption is valid is, of course, unknown. However, the importance of the results (*J10*) remains because they do strongly suggest that, in FIK, reactions are being studied at energies comparable to those encountered in gas-phase kinetics of neutrals (i.e., thermal energies).

The FIK technique has been applied to molecular ion decompositions of aliphatic esters (*J8*), *n*-pentyl-benzene (*J7*, see also *J103*), tetralin (*J41*), hept-1-ene (*J93*) isobutyl alcohol (*J91*), benzylcyanide (*J96*), decalin-1,4-diols (*J28*) and 3-phenylpropanol (*J98*). FIK results for ^{13}C- and D-labeled 1,3-butadiene show that hydrogen randomization is complete within approximately 10 ps, whereas skeletal isomerizations to ring structures are much slower and must compete with dissociations (*J74*). Results for ^{13}C- and D-labeled butenes suggest that at short times (10–100 ps) intramolecular energy is *not* randomized prior to decomposition (*J54*). Mechanisms proposed for the loss of C_2H_2O and C_3H_4O from the 3-phenylpropanal ion are analogous to the McLafferty rearrangement (*J105*); mechanisms for hydrogen exchanges are also advanced (*J105*).

Some general questions concerning appearance energies and FIK are raised by work on hexanal and 3-methylpentanal (*J14, J55*). Appearance energies show that *at threshold* the neutral accompanying formation of $(C_4H_8)^{+\cdot}$ is acetaldehyde, whereas vinyl alcohol is expected according to the classical McLafferty rearrangement mechanism. It is suggested (*J14, J55*) that there are at least two distinct mechanisms for formation of $(C_4H_8)^{+\cdot}$: a minor low-energy pathway detected at threshold leading to acetaldehyde and the established McLafferty rearrangement which is predominant in the ps–μs time-range following FI. The translational energy release obtained from metastable peaks has been found to be the same following FI and EI for a number of decompositions (*J52*).

The nature of ionization processes involved in FD mass spectrometry has become rather controversial during the past year (*J4, J5, J30*). Much of the disagreement would seem to be a matter of semantics and has been exacerbated by consistently poor expression of ideas. Beckey and Rollgen (*J5*) make the point that *the electric field is essential in FD* and, in the case of molecular ions ($M^{+\cdot}$), this seems to be generally realized and accepted (*J13*). There is, however, still a body of opinion maintaining that "cationization or protonation can occur in the absence of an electric field" (*J13*). The argument advanced is that the electric field cannot be essential, since techniques such as laser desorption and plasma desorption produce the same protonated and cationized species. What seems to be overlooked is that these other techniques also have very substantial local electric fields in their ionization regions—laser electric fields can of course be extremely high. Results (*J5*) with FD quadrupoles show that in FD the protonated and cationized species cannot, in fact, be desorbed unless potentials of the order of kV are applied. In the opinion of the reviewers, the electric field is not merely essential but the dominating factor in FD, since it is the field which makes charge separation thermodynamically feasible. Charge separation can take the form of electrons tunneling out of molecules, proton transfers (facilitated by tunneling) between molecules, separation of the oppositely charged ions in electrolytes, and so on.

Certain samples can leave the surface of an FD emitter (*J30, J57*) in the form of droplets (*J27*); however, the molecules in these droplets do not contribute to the signal in the mass spectrum (*J27*; see also *J95*). Using an optical microscope, Giessmann et al. (*J27*) have actually observed droplets of sucrose leaving an emitter at field strengths below those necessary for formation of molecular or pseudomolecular ions.

Measurement of cluster ions from alkali halides indicates an influence of ion mobilities on the desorption characteristics (*J70*). The presence of polyhydroxyl components on FD emitters greatly affects desorption of carboxylates (*J106*). Both polyphosphoric acid (*J43*) and "polymerically saponified lithium salts" (*J73*) on bare 10-μm tungsten wires allow formation of ions from gaseous samples, at field strengths below the threshold for FI.

An argon ion laser has been used, in place of the emitter current, to heat the FD emitter and provides improved sensitivity and greater reliability at high resolution (*J82*). The technique has allowed the molecular ion of vitamin B_{12} to be detected (*J82*).

Among the many compounds measured by FD using heating currents are surfactants (*J44*, *J63*), low molecular polymers (*J36*) and substances such as plasticizers important in polymer chemistry (*J37*), lipids (*J68*), peptides (*J22*, *J66*), nucleotides (*J47*), glycosides (*J20*, *J81*), various pesticides (*J83*, *J88*), herbicides (*J108*) and biocides (*J78*), antibiotics (*J60*), macrocyclic polyesters (*J109*), chlorophyll (*J16*), carboxylic acids (*J107*), reduction product of a 1,2-benzodithiole-3-thione (*J64*), coal liquefaction products (*J110*), derivatives of oleuropein and ligustroside (*J84*) and inorganic coordination complexes (*J23*, *J24*, *J104*). FD has been used to determine isotope ratios of metals (run as their salts) (*J33*), and to quantitate Li in body fluids (detected at μmol L^{-1} level) (*J38*).

FD with emitter current programming has been applied to analysis of multicomponent mixtures (*J86*), and selected ion monitoring of berberine chloride under FD has given a detection limit of 10 ng mL^{-1}. Using signal averaging, picogram quantities of choline and acetylcholine have been detected by FD (*J40*). Signal averaging has also been used to improve precision of mass measurement (*J65*). Curie-point pyrolysis and FD have given useful spectra from the polysaccharide glycogen (*J80*).

The FD mass spectra of pyridinium salts have been interpreted with the aid of D and ^{13}C labeling (*J35*); an ion of mass equal to that of the (cation + 1) is shown *not* to be the protonated "molecular ion" (*J35*). Multiply charged ions were observed in the FD mass spectra of basic peptides (*J32*). The ions were of the general formula $[M + nH]^{n+1}$, and n would take values up to and including the net number of basic sites in the peptide (i.e., n = no. of basic amino acids − no. of acidic amino acids) (*J32*).

In order to obtain structural information, field desorbed ions have been fragmented by collision with neutral gas (*J67*, *J71*, *J87*, *J100*, *J102*). Two groups employ a collision cell in the source, so that both magnetic and electric sector fields are scanned ("linked scan") (*J87*, *J100*). This approach of combining FD and collisional activation (CA) has been applied to complex cations from salts (*J100*, *J102*) and to cationized saccharides (*J67*, *J71*, *J87*). Straub and Burlingame have been able to elucidate the structure of polynucleotide derivatives using the method (*J87*).

There is also considerable interest in FI mass spectrometry (i.e., gaseous sample) as an analytical method. It has been suggested that, for the analysis of mixtures, FI with its absence of fragmentation is 1–3 orders of magnitude more sensitive than EI (*J2*). Measurements of relative sensitivities of saturated hydrocarbons suggest that high source temperatures should be used for quantitative analysis by FI (*J77*; see also *J45* and *J76*). FI is recommended as a method for locating double bonds in alkenes (*J42*), and fragmentation of alkenes via simple bond cleavages can be induced using tip emitters (field dissociation) (*J69*). The intramolecular surface effects have been investigated for alkane/alkyne mixtures (*J75*) and for hex-1-ene/water mixtures (*J61*). FI mass spectra have been reported for phosphates (*J34*, *J51*) and amino acid derivatives (*J89*).

FI mass spectra have been obtained with samples such as acetone and methanol at emitter temperatures as low as 145 K (*J25*). The mass spectra show series of unprotonated cluster ions (M^+, $2M^+$, $3M^+$, etc.) which originate from liquid layers on the emitter (*J25*). Exchange between gaseous halogoalkanes and alkali halides on an emitter surface has been clearly demonstrated (*J72*). The origin of doubly charged ions from hept-1-ene (*J92*) and acetophenones (*J29*) has been investigated. ^{13}C and D labeling has been exploited to elucidate mechanistic aspects of the FI mass spectra of hept-1-ene (*J94*).

METASTABLE IONS

The translational energy released during the dissociation of a transition state is one property of chemical reactions which can be measured by mass spectrometry with a combination of convenience, accuracy, and scope (in terms of accessible reactions) not obtainable with any other technique, including molecular beams. The subject has been an active area of enquiry during the past two years and has been reviewed (*K12*).

It is usual to distinguish two sources of the released energy (viz., nonfixed energy of the transition state and reverse activation energy (*K29*, *K47*), although a conclusion (*K28*) that the energy release for $(CH_3OH_2)^+ \rightarrow (CH_3O)^+ + H_2$ decreases as internal energy increases, questions the validity of this distinction. It should be noted that there are coincidence measurements on quite a number of other reactions showing energy release increasing with internal energy (for example, *G56*). Translational energy releases measured with a time-of-flight instrument have been reported (*K40*).

A dynamical theory of the partition of the reverse activation energy provides a quantitative relationship between transition state geometry and energy release (*K19*), and has explained the substantial isotope effects on the energy release in $(CH_2OH)^+ \rightarrow (CHO)^+ + H_2$ (*K54*). According to this dynamical approach, many intramolecular rearrangements are likely to partition only small proportions of reverse activation energies into translation (*K21*), which to some extent runs counter to the rule-of-thumb that reactions involving slow isomerization prior to dissociation give "broad" metastable peaks (*K6*). This type of "broad" peak very possibly arises because the nonfixed energy is unusually large [due to a slow rise of $k(E)$ with internal energy E].

This dynamical theory (*K19*) predicts that exoergicity ("early" transition states) should tend to disfavor translational energy release while endoergicity should favor such energy release. These predictions are in accord with conclusions of Schaldach and Grütsmacher (*K57*; see also *K56*) who have studied the energy release in the rearrangements of variously substituted benzalacetones to form the 2-methylbenzopyrilium ion (see also *K23*). They find that the proportion of reverse activation energy partitioned into transition is 0.2–0.3 for exoergic reactions and 0.9–1.0 for endoergic (thermoneutral) reactions (*K57*).

Predictions of statistical theories with respect to partition of nonfixed energy have been drawn out (*K26*) and the energy released in the loss of CO from $(CH_2{=}C{=}O)^{+\cdot}$ considered from this point of view (*K26*). Detailed theoretical treatments of the energy release in the loss of C_2H_4 from $(C_6H_5OC_2H_5)^{+\cdot}$ (*K5*) and the loss of H_2 from $(C_3H_5)^+$ (*K37*) have been made. A Monte Carlo method of calculating energy release distributions $T(E)$ from metastable peak shapes has been described (*K30*).

Consideration of energy releases in relation to appearance energies can be highly effective in identifying structures of product ions (*K32*, *K68*). For example, the appearance energies for the formation of $(C_3H_3)^+$ from C_3H_3I species indicate that either the product is the propargyl ion and there is no reverse activation energy or the product is the cyclopropenium ion and there is a significant reverse activation energy (*K28*). The metastable peaks show that there is little energy released (*K28*). Knowing the nature of energy partition in some similar compounds, it is concluded that the reaction cannot have a significant reverse activation energy and, hence, that the product is the propargyl ion (*K28*).

That the outcome of competition among decomposition of metastable ions is often determined by their relative activation energies has been used extensively to rationalize the chemistry of small organic ions (*K6*, *K13*, *K14*, *K60*, *K62*). The approach seems to involve making an intelligent supposition as to the structure of the transition state in the rate-determining step of the decomposition and then estimating the heat of formation of the supposed structure. The "broadness" of the metastable peak is used as a guide to the form of the transition state. The term "reacting configuration" is frequently employed in these papers; however its precise meaning is not clear to these reviewers.

The schematic diagrams, referred to as "potential energy profiles", show heats of formation of isomers, identify those isomers, which interconvert and which ones decompose, and indicate estimated (or measured) activation energies [for example, $(C_4H_9O)^+$ (*K8*, *K11*), $(C_3H_8N)^+$ (*K10*)]. As such they are a very effective method of conveying information. The name, could, however, be misleading, and the term "schematic potential energy diagram", which has been used for this same type of diagram (*K3*), seems far less objectionable. Mechanisms for the decomposition of $(C_3H_7O)^+$ have been reexamined and revised (*K31*).

Orbital symmetry rules are quite often applied to reactions of gaseous ions (*K7*), although the fallability of such qualitative arguments has been demonstrated by calculations on $(CH_3O)^+ \rightarrow (CH_2OH)^+$ (*K58*). The general point is that if the geometry of a gaseous ion is not known, its molecular symmetry is uncertain. Therefore, orbital symmetry is uncertain and the simple rules become unreliable (Consider also *F9*).

A mechanism for keto–enol tautomerism prior to CO loss from phenol ions involves 1,3 hydrogen shifts (*K55*); however, this has been questioned and mechanistic arguments in favor of successive 1,2 shifts have been advanced (*K61*). Decomposition of enol ions via keto structures has been discussed elsewhere (*K49, K51*). Energy releases for decompositions of small ions containing sulfur have been reported (*K16, K24*; see also *K18*) as have energy releases for chlorinated biphenyls (*K25*).

Metastable ion studies are often complemented by collisional activation (collision-induced decomposition) measurements, since the latter often allow the structures of product ions from (formally similar) reactions occurring in the source to be determined (*J103, K34, K59, K63*).

Kinetic isotope effects have been determined from metastable peak heights (areas), not only for hydrogen (*K2, K66*) but also for chlorine (*K69*). Hydrogen isotope effects on methyl loss from the methyl isobutyrate ion reveal that a hydrogen migration accompanies the dissociation (*K64*; see also *K65*). Specific isotopic labeling with deuterium and measurement of metastable peak heights have elucidated reaction mechanisms of $(C_4H_9O)^+$ (*K36*), acetoxytetralin ions (*K67*), diphenylpropane ions (*K39*), and propionic acid ion (*K52*). In the (ω-alkylphenyl)benzenium ion, repeated ring-to-ring hydrogen transfers occur without involving the linking aliphatic chain (*K38*). Labeling with ^{13}C has demonstrated that loss of C-2 (or C-3) from the butane ion as methyl or methane is concerted, in the sense that isomerization to 2-methylpropane ion is not involved (*K33*). Exhaustive labeling with ^{13}C and ^{15}N has been used to elucidate mechanisms of decomposition of monocyanopyridines (*K50*). Metastable peaks with butanoic acid ions have been interpreted in terms of involvement of isolated electronic states (*K53*). The criterion of "competing metastable intensities" is still a useful and effective application (*K9, K17*).

A series of papers has shown the very considerable advantages of representing metastable peaks as ion currents as a function of two instrumental parameters (as opposed to one such as accelerating potential or magnetic field) (*K41–K46*). The sensitivity of metastable peak shapes to instrumental parameters in a reversed geometry instrument has been discussed (*K35*), as have the possibilities for interfering peaks (*K1*; see also *K4*).

Metastable peaks with negative ions have been studied (*K20, K66*), as has decomposition of doubly charged ions (*K48*). A reversed geometry instrument has been used for analysis of sidechains from steroids (*K15*).

MASS SPECTROMETRY/MASS SPECTROMETRY

The term "mass spectrometry–mass spectrometry (MS/MS)" has begun to be used to mean experiments in which the ions in a mass-selected beam are fragmented by collision and the ionic fragments so formed are mass analyzed (*L22, L30, L35*). In this way, a mass spectrum can, in principle, be obtained for each ion in a mass spectrum. In reality, most measurements at the present time are made with reversed-geometry double-focusing mass spectrometers (MIKE, CID, or whatever), and therefore, fulfill this aim of a "mass spectrum of a mass spectrum" only very crudely. The primary beam is not velocity-focused, so that beams of different ion masses may overlap at their direction-focus, and the second spectrum is a translational energy spectrum, typically with very broad peaks. The MS/MS approach should receive considerable impetus from the tandem mass spectrometer consisting of two large double-focusing mass spectrometers in-line, which is being constructed by McLafferty and coworkers (*L34*). The double-focusing capability of the first stage means that the primary ion beam is truly mass-selected, and that of the second means that it is the masses of the fragment ions from collision which are measured (i.e., a genuine mass spectrum, with sharp peaks). We use the term MS/MS here for all the various types of collision experiments using single double-focusing mass spectrometers, because this avoids having to distinguish and decide among MAMIE, DADI, MIKE, IKE, PCE, and so on.

One advantage claimed for MS/MS, compared to chromatographic techniques, is speed of analysis (*L14, L25, L35*). In analyzing mixtures, "soft" ionization techniques can offer advantages over EI in the initial ionization, and chemical ionization (CI) in particular but also field ionization (FI) have been used quite widely (*L13, L22, L28*). The physics of ion beam collision processes has been covered in some depth in the book edited by Cooks (*L7*). Biochemical applications (and other aspects) have recently been reviewed by Beynon and Caprioli (*L1*).

The use of three quadrupoles in-line has also been advocated for MS/MS by Yost and Enke (*L50–L52*). The first quadrupole mass-selects the ion, the second acts as the collision chamber and the third mass-analyzes the ionic products after collision (*L52*). Such an instrument does give a true "mass spectrum of a mass spectrum". Strong claims as to efficiency of collision-induced decomposition, efficiency of collection of ionic fragments and overall sensitivity have been made for the triple quadrupole arrangements (*L54*). It is reported (*L50*) that 120 fg of nitrophenol can be analyzed with a triple quadrupole (compared with 10 pg using CI on a reversed geometry double-focusing mass spectrometer) and that the low-energy collision process produces 400 different fragment ions from nonan-4-one. The efficiency of the high-energy collisions in magnetic sector instruments has also been discussed (*L21*).

Tandem mass spectrometers offer control over the translational energy as well as the mass of the ion selected for collision, and over the years much detailed data have appeared concerning low energy collisions. Comparison of results from triple quadrupoles with these data might elucidate the nature of the processes occurring in the quadrupole. In particular, it would be valuable to confirm that these quadrupole results are largely free of artifacts and that the rf fields do not influence the collision cross-sections. More recently, tandem instruments have been applied to reactions of negative ions of ozone (*L29*) and to reactions of alkyl cations with silanes (*L15–L17*).

Boerboom and colleagues (*L30*) have constructed a tandem mass spectrometer for collision studies, which makes use of sophisticated ion optics and detection techniques. Use of a channelplate (with an optical converter) means that ions over a wide and variable ("zoomable") mass range can be detected simultaneously. The ionic fragments from the collision are analyzed in a magnetic sector, so that post-acceleration (after collision) alleviates the problems of the ions' energy spread and gives high collection efficiency. Overall, the system offers very high sensitivity, reasonable mass resolution (600) and the possibility of studying very fast processes (as might be encountered in FD).

Eye-catching results have been obtained by directly pyrolyzing biological samples (coca leaves, salmon sperm DNA) into the ion source on a probe and investigating structures of ions obtained from the pyrolysis products by the MS/MS technique (*L22, L23, L42*). The alkaloid coniine has, for example, been identified in hemlock on the basis of the mass spectrum of the m/z 128 ion (protonated molecular ion) (*L23*). Detection limit is placed at 1 to 10 ng for a number of alkaloids (*L23*). The energy spreads of both the primary beam and the fragments from collision vitiate the quality of the spectra (*L22, L23, L42*). More than this, however, certain of the results with salmon sperm DNA have been shown to be artifacts of pyrolysis (*L45*), and such artifacts must be a general possibility.

Particular mention needs to be made of negative chemical ionization (CI) as a source of ions for collision-induced decomposition, because under appropriate conditions negative CI affords unparalled sensitivity (see below). Cooks and colleagues (*L5, L24, L32*) in particular have made effective use of negative CI for MS/MS experiments. Negative EI has also been used as a source of ions for collision-induced decomposition by Bowie and colleagues (*L2, L6*).

Charge reversal in which the *positive* ions formed in the collision of *negative* ions with neutral gas are measured is proving to hold both fundamental (*L41*) and analytical significance (*L2, L32*). This technique (also called "charge stripping") has been shown to be a welcome additional tool for ion structure studies (*L3, L4*). Howe et al. (*L19*) have shown how measuring the charge in translational energy

during charge reversal constitutes a method for determining electron affinities. Collision-induced decomposition of (SF_6^-) has been used to determine thresholds for formation of $(SF_5)^-$ (*L40*).

A double-focusing mass spectrometer has been modified to allow measurement, albeit somewhat crude (*L26*), of angular distributions of the fragment ions formed through collision (*L11*). The mass spectrum is dependent upon scattering angles due at least in part to the energy deposition depending upon angle (*L27*).

MS/MS as a method of identifying stable ion structures [collisional activation (CA) of collision-induced decomposition (CID)] has been applied to numerous compounds, including substituted cyclopropanes $[(C_3H_5CO)^+]$ (*L44*), 1,2-cyclohexanediols and cyclopentanecarboxaldehyde (*L53*), pyrones $[(C_4H_4O)^+]$ (*L18*) and aromatic nitro compounds (*L31*). The structures of $(C_7H_7)^+$ (*L36, L37*) and $(C_6H_8)^+$ (*L50*) have been further elucidated. MS/MS has evidenced the existence of aziridine ions $(CH_2CH_2NH_2)^+$ (*L52*), ethylene-chloronium and methyl-chlorocarberium ions (*L38*), and both $(CH_3COOCH_3)^+$ and $(CH_2{=}C(OH)OCH_3)^+$ (*L43*). The method has been applied to isobaric ions, for example $(C_4H_5O)^+$ and $(C_5H_9)^+$ (*L51*). Interpretation of MS/MS measurements on the small ions $(CH_3O)^+$ and $(CH_3S)^+$ has been supported by ab initio molecular orbital calculations: $(CH_2{=}SH)^+$, $(CH_3S)^+$, and $(CH_2{=}OH)^+$ exist as does a weakly bound structure $(H_2{\cdot}HCO)^+$ (*L8–L10*) (see also *K58*). The mass spectra resulting from collisional fragmentation of $(C_6H_5CO)^+$ ions depend upon internal energy (*L39*), sounding a caveat for ion structure studies. Differences between the fragmentation of protonated aromatic ions induced by collision and that induced by photon impact have been observed, and are interpreted in terms of an involvement of rotational energy (*L12*). A combination of CA and photodissociation has shown that the decomposition of butyrophenone ions can be explained without invoking isolated electronic states (*L20*).

ION CYCLOTRON RESONANCE (ICR)

Fourier transform ICR spectroscopy remains one of the most promising areas of ICR, particularly from the viewpoint of analytical chemistry (*M17*). The method offers more rapid recording of mass spectra, better sensitivity, higher mass resolution, and an extended mass range (to higher masses), as compared to conventional scanning ICR (*M19, M31*). According to a recent review, Fourier transform ICR appears to be on the threshold of assuming a major role in analytical chemistry (*M42*), and it is predicted (*M28*) that it will develop into a high-performance mass spectrometric technique (sample pressures as low as 10^{-9} Torr have been used). Among other instrument-related developments are signal modeling based on a rotating electric monopole (*M18*), a determination of nonreactive ion–molecule collision frequencies (*M32*), and a theoretical investigation of coupling between the ion's cyclotron resonance and its various angular momenta (*M23*). ICR has been reviewed (*M26*).

Numerous gas-phase equilibrium measurements have been reported using ICR, and determination of basicities (*M6*), acidities (*M7*), and electron affinities (*M29*) have all been recently reviewed. Reading ICR papers on equilibria, it is noticeable that the question of ion structure does not always receive close attention—there is a tendency to assume that the "obvious" structure is the right structure. The hydration of pyridines has been studied in close detail (*M3*). Amides and imidates are among the groups of compounds recently investigated in basicity measurements (*M5*). Both the basicity and the acidity of glycine have been determined (*M30*). The usefulness in the gas phase of the concept of "hardness of bases" has been looked at (*M11*). The scale of acidities in the gas phase has been summarized and its construction discussed (*M8*), and effects of substituents and solvation assessed (*M9*). A table of experimentally determined electron affinities appears in the review (*M29*) mentioned above. Equilibrium constants can be measured for electron-transfer reactions by trapping long-lived negative ion radicals (for seconds) (*M34*), and so a scale of relative electron affinities can be obtained directly.

The fragmentation by electron impact of organic ions trapped in an ICR cell has been described and advanced as an analytical method (*M16*).

ICR has been widely used both to measure specific reactions (*M15, M20, M22, M33*), particularly those bearing analogy to solution chemistry (*M4*), and to elucidate ion structures. The hydrolysis of esters has been studied using ^{18}O labels (*M38*), for example. A tandem instrument consisting of a magnetic sector and an ICR cell has been used to study specific reactions of allyl ions (*M27*). Intramolecular kinetic isotope effects on proton transfer have been found to be normal ($k_H/k_D > 1$) or inverse ($k_H/k_D < 1$) depending on whether the reaction is exothermic or endothermic (*M41*). A detailed study of the properties and reactions of ketene (ions) has been made using ICR (and also photoionization mass spectrometry) (*M40*), and ion–molecule reactions of nitriles have been investigated (*M14*). There is evidence that the cyclobutene radical cation undergoes electrocyclic ring opening to give the 1,3-butadiene ion with an activation energy of <30 kJ mol^{-1} (*M24*). A relatively new and very active area of research concerns ion–molecule reactions of inorganic and organometallic species (*M1, M13, M36, M37*). For example, reactions of $(Li)^+$ and $(Na)^+$ with alkyl halides and alcohols have been the object of one ICR study (*M2*).

It has been shown using ICR that $CH_2{=}O^+{-}CH_2$ is a stable gas phase entity (*M12*), and 1-methoxycyclopropyl and 2-methoxyallyl cations have been shown to be distinct stable species (*M39*). It has been found that little intramolecular hydrogen rearrangement occurs within long lived allyl anions (*M21*). Stable ion structures of $(C_2H_4Cl)^+{\cdot}$ and $(C_2H_4Br)^+{\cdot}$ have been investigated by ICR (*M10*), as has the isomerization of $(C_4H_9)^+$ species (*M35*) and formation and structure of protonated dimers of carbonyl compounds (*M25*).

CHEMICAL IONIZATION AND OTHER HIGH PRESSURE TECHNIQUES

Chemical ionization (CI) has been recently reviewed (*N26, N39, N48*). There is a growing interest in the analytical capabilities of negative CI (*N6, N17, N46, N51, N62*), which in favorable circumstances can afford sensitivity two or three orders of magnitude greater than that obtainable with positive CI (*N21*). Positive and negative CI mass spectra can be measured "simultaneously" using a quadrupole mass filter, by simply pulsing the polarities of source potentials (discussed in Ref. *N26*). Positive and negative CI spectra of diols, by providing information of gas-phase basicities and acidities, allow configurational isomers to be distinguished (*N63*) (see also Ref. *N62*).

A vespel probe for "in-beam" CI has been described (*N9*), although some doubt has been expressed as to whether ionization actually occurs on the probe surface (*N10*). If the "in-beam" method owes its success to enhanced volatility (of the neutrals) (*N10*), other results (*N20*) demonstrating the importance of the precise position of the probe within the source are less easily explained. CI has been effectively applied to analysis of pyrolysis products of polymers (*N53*).

A CI mass spectrometer incorporating a drift tube (40 mm) has been described and used to analyze esters (*N47*). An instrument for atmospheric pressure ionization incorporates a drift region, in which clusters can be broken up by collision (*N29*). Relative rate constants for reactions of $(CH_5)^+$ and of $(C_2H_5)^+$ with a series of compounds have been determined by using GC/CIMS (*N22*).

The reduction of ketoacids by the reagent gas provides a basis for differentiating isomers (*N24*). ND_3 used as a reagent gas provides a means of determining the number of active hydrogens in a compound (*N34*). The addition of small amounts of pyridine to isobutane or ammonia reagent gases is advocated for analysis of glucuronides ($(M + 80)^+$ peaks are seen) (*N27*). Cyclohexane has been shown to be an effective reagent gas in the analysis of fossil fuels, when combined with photoionization (for the initial ionization) (*N54*).

Among the very many processes identified and studied by CI mass spectrometry during the past two years are loss of water and skeletal rearrangement in protonated ethers (*N15*), dehydration of aminoalcohols (*N35*), retro-Diels-Alder reaction in diones (*N65*) (see also Ref. *N64*), loss of water from protonated cyclohexanols (*N18*) and from protonated aldehydes (*N1*), and loss of CO from phenylpropenylether (analogy with Claisen rearrangement) (*N28*). Polyamines (*N60*), diaminoacids (*N61*), and aryl ureas (*N5*) have been measured by CI mass spectrometry. It has been shown that peaks 30 mass

units below the $(MH)^+$ peaks in the CI mass spectra of aromatic nitro compounds are *not* due to loss of NO from the ion, but result from a thermal process (*N4*). The appearance of odd-electron fragments in the H_2 CI mass spectra of substituted halobenzenes sensitively reflects the thermochemistry of the systems, and leads to estimates of heats of formation of substituted phenyl cations (*N33*).

The thermochemistry of biological compounds of low volatility, such as nucleic bases (*N43*), has been investigated using a pulsed high-pressure mass spectrometer in a CI mode. Proton affinities have been determined for amino-acids (*N45*). The same technique has given enthalpy charges for clustering of HCN and CH_3CN about $(H)^+$ (*N41*), and bonding energies of association ions of aromatic compounds (*N44*) (see also Ref. *N42*). Using an apparatus especially designed for the purpose, enthalpy and entropy charges have been obtained for clustering of ammonia about $(Li)^+$ and $(Na)^+$ (*N8*) and hydration of $(CO_3)^-$ and $(HCO_3)^-$ (*N30*). Properties of ion clusters have been discussed in relationship to heteromolecular nucleation (*N7*). The solvation of $(H)^+$ (*N37*) and the hydration of pyridinium ions (*N11*) have also been investigated.

The flowing afterflow technique and related flow tube methods have recently been reviewed (*N55*). Reactions of negative organic ions have been investigated by the technique (*N12–14, N38*) (see also Ref. *N52*). Proton affinities have been reported for HCHO, HCN and H_2S (*N19*) and reactions of $(H_3O)^+$ studied (*N3*).

Rates of three-body ion–molecule reactions, calculated on the basis that internal energy is randomized in the collision complex, agree with experiment (*N25*). The significance of angular momentum in ion–molecule reactions and in unimolecular decomposition is emphasized in two theoretical treatments (*N2, N59*).

Using a tandem mass spectrometer, Sunner and Szabo (*N56, N57*) have elucidated the reaction chains initiated by different electronic states of molecular ions [such as $(H_2O)^+\cdot$]. In studies of thermal ion–molecule reations, metastable peaks have been observed for decomposition of long-lived intermediates (*N32*) [such as $(CH_2COHCl)^+\cdot$] and inverse hydrogen isotope effects found for dimerization in propylacetate (*N31*). Rate constants have been determined for low energy ion–molecule reactions of $(O)^-$ (*N16*) (see also Ref. *N49*). Formation of $(Cl_3)^-$ has been investigated (*N50*).

A coincidence technique has been developed for the products of an ion–molecule reaction and threshold electrons (from the ionization forming the reactant ion) (*N58*), allowing ion–molecule reactions of state-selected ions to be studied. The reactions of selected vibrational levels of $(C_2H_2)^+\cdot$ with CH_4 have been investigated, giving the dependence of reaction rate on vibrational energy (*N23*). Ion–molecule reactions in 2-methylpropene have been looked at using photoionization (*N36*). A detailed analysis has been made of the assumptions involved in time-resolved (arrival times) measurements in high-pressure mass spectrometry (*N40*).

BIO-OLIGOMERS AND THEIR CONSTITUENTS

Amino Acids, Peptides, Proteins and Sequencing. The fragmentation of trimethylsilyl (TMS) amino acids upon electron impact (EI) was investigated to provide a spectral basis for further studies of physiological samples, and to elucidate the possibility of ultramicrodetermination of amino acids by mass fragmentography; the results suggest that these derivatives can be used for the above purposes (*O18, O25*). Analysis of amino acids as *N*-dithiocarbamic derivatives by means of EI and field ionization (FI) mass spectrometry was reported (*O39*). These derivatives were demonstrated to be sufficiently volatile for mass spectral analysis using the direct inlet probe. The EI spectra exhibit relatively intense $M^+\cdot$ peaks and structurally diagnostic fragment ions; the FI mass spectra show abundant $M^+\cdot$ ions and little fragmentation. An easy method for the identification of amino acids in a mixture by mass spectrometry without using GC/MS is described (*O33*). After separation on a classical amino acid analyzer without prior purification, amino acids were esterified with methanol in dimethoxypropane containing HCl at ambient temperatures and the resulting methyl esters were identified by mass spectrometry. The determination of steric purity of amines and amino acids by GC-chemical ionization (CI) mass spectrometry is reported (*O47*). The negative ion mass spectra (2–4 eV) of 20 free amino acids were measured and compared with positive ion mass spectra at 6–16 eV (*O44*). CI and EI mass spectra were employed for the detection of amino acids and fatty acids in blood; CI mass spectrometry proved to be more advantageous than EI mass spectrometry in analyzing mixtures. Ammonia CI of some free amino acids and underivatized peptides were examined and extensive formation of solvated-protonated species was observed, as well as associated protonated peptides [up to $(4\ M + H)^+$ in some cases] (*O15*). The observed association reactions with rapidly heated samples present problems in the analytical use of this technique.

TMS derivatives of 17 neutral and acidic amino acids were analyzed by a GC/CIMS/computer system; the use of MH^+ ions in the mass spectra made it easy to identify and detect the number of TMS substituents (*O40*). The isobutane CI spectra of TMS amino acids and some oligopeptides have been discussed (*O10*). The CI mass spectra of 16 amino acid thiohydantoins were examined using isobutane or ammonia as reagent gases (*O32*). Except for a few cases, including some aromatic amino acids, the CI spectra were much simpler than the corresponding EI spectra. Therefore, the main components in the amino acid thiohydantoin mixture were easily detected by CI mass spectrometry. The CI mass spectra of fluorescamine and fluorescamine amino acid derivatives were shown to exhibit MH^+ and adduct ions as the major ions formed (*O38*). Secondary ion mass spectrometry was applied to amino acid analysis (*O8, O17*). The tranesterification of *N,O*-trifluoroacetyl hydroxy amino acids butyl esters with $(EtO_2C)_2$ to give *N*-trifluoroacetyl-*O*-carbethoxy derivatives was studied by GC/MS (*O20*). A comparison of fragmentation of methionine in field desorption (FD) mass spectra with the fragmentation pattern of the same compound under EI, CI, and Curie point pyrolysis is given (*O43*). The methane CI mass spectra of α,ω-diamino acids, ω-amino acids, cyclic and acyclic α-amino acids, and corresponding methyl esters were studied (*O46*). Structural factors which select between decarboxylation and lactam, lactone, and cyclic amino acid formation are estimated. The prevalence of reactions correlates with the product ion stability. The detection of glutamine and glutamic acid in biological fluids by GC/MS is described (*O11*) in which the amino acids are derivatives to *N*-trifluoroacetyl *n*-butyl esters; equations are presented for separately detecting glutamic acid and glutamine (or aspartic acid and asparagine). Mass spectra of 21 metabolically important acylglycines (*O34*) and 2,4,5-trichlorophenoxyacetic acid-amino acid conjugates have been reported (*O7*).

Application of various mass spectral methods to analysis of dipetidyl aminopeptidase digest continues to attract attention. A review (23 references) on polypeptide sequencing by dipeptidyl aminopeptidases digestion, trimethylsilylation, and GC/MS has been published (*O24*). Krutzsch and Pisano studied separation and sequencing of dipeptides using GC/MS of their TMS derivatives; a sufficient variety of samples (ca. 200) has been examined to establish predictable fragmentations which allow the identification of all 400 possible dipeptides (*O23*). The CI and EI mass spectra were compared for more than 40 TMS dipeptides (*O22*). The CI mass spectra of TMS dipeptides typically contain three ions of high abundance used for dipeptide identification: a sequence-detecting ion and two molecular weight-detecting ions. The intensity of the molecular weight-detecting ions relative to that of the ion that characterizes the N-terminal residue (β-cleavage ion) is greater in the CI mode than in the EI mode. Because the available intensity of β-cleavage ion is similar in both modes, use of the CI mode will extend the lower limit of TMS dipeptide identification. The GC and mass spectrometric behavior of more than 120 different *N,O*-perfluoropropionyl methyl esters of dipeptides was investigated using both EI and CI; these techniques enable the unambiguous identification of dipeptides in mixtures (*O37*). The fragmentation of *N*-decanoyl dipeptide methyl esters under EI was carefully studied by Akhrem et al. (*O1–O6*). It was demonstrated that the EI and FD mass spectra of unprotected dipeptides can be used to detect the primary structure and molecular weight of the peptides (*O27*). The mass spectra are reported of 36 triazine derivatives of amino acids and peptides which incorporate the C-terminal in the triazine ring. Characteristic fragments indicating the presence of the triazine

ring were observed which, when used as a marker, enabled estimation of the C-terminal of peptides. In dipeptides, both terminals could be determined simultaneously (*O29*).

Several reviews on the application of mass spectrometry in protein structure determinations have been published (*O9*, *O26*, *O41*, *O48*).

The simplified method for calculation of GC retention indexes of perfluorodideuteroalkylated peptide derivatives has been presented by Van de Graaf et al. (*O42*). The more accurate retention index increments assigned to the amino acid residues can be calculated from experimental retention indexes using a standard least squares procedure, which can be implemented in a GC/MS/computer program for the identification of the peptide derivatives. The key steps in an automated system for polypeptide sequencing using a liquid chromatograph/mass spectrometer/computer system were tested with mixtures containing up to six model peptides. At the low nanomole level, complete sequencing was possible for most but not all mixtures. Interpretation of results was complicated by side reactions in the derivatization process; these side reactions must be eliminated to reduce ambiguities arising from degradation of larger peptides, and to decrease the amounts required to the subnanomole level (*O12*). An approach to the differentiation of leucine and isoleucine residues in electron impact mass spectra of peptides has been proposed by Waern and Falter (*O45*). A new procedure for reduction of oligopeptides to amino alcohols with borane was described (*O13*). The procedure was employed for reduction of permethylated peptides; the derivatives prepared this way are more volatile than the corresponding permethylated derivatives. As little as 10–100 nmol of these peptide derivatives were sequenced using mass spectrometry (*O30*). Nitrile elimination and hydrogen rearrangement upon EI in Schiff base peptide esters were examined with the aid of deuterated derivatives (*O19*).

Tracing the generation of consecutive ions stepwise by direct analysis of daughter ions by mass spectrometry leads to the successful sequencing of amino acids in tripeptides (*O36*). CIMS in combination with structure construction logic was applied to the structure elucidation of neurotensin (*O49*). Determination of the amino acid sequence of the C-terminal cyanogen bromide fragment of myoglobin from bottle nosed dolphin by mass spectrometric peptide mixture analysis was reported by Roepstorf (*O35*). The sequence of 102 amino acid residues from N-terminus and that of 39 amino acid residues from the C-terminus of bacteriorodopsin were detected by a combination of enzymatic digestion, mass spectrometric peptide sequencing, and automated Edman degradation (*O16*). Several attempts to apply FD mass spectrometry to the sequence analysis of underivatized oligopeptides did not give very encouraging results. This technique is suitable for peptide molecular mass detection with consumption of picogram quantities of material; derivation of other structural information is not readily achieved (*O14*, *O28*). Multiply charged ions up to $(M + 4)^{4+}$ were observed in the FD mass spectra of five different peptides containing basic amino acids, and the relationship between the charge-multiplicity and the number of basic sidechains was determined (*O21*).

Purines, Pyrimidines, Nucleosides, Nucleotides, and Nucleic Acids. The mass spectra of 8 methyl-substituted uracils show that these compounds undergo retro-Diels-Alder reaction with elimination of HNCO or MeNCO (depending on substitution at N-3), followed by sequential loss of CO and H or vice versa. The extent of other fragmentations depends on the location and number of methyl groups (*P20*). A method, combining GC/MS with multiple specific ion monitoring was developed for detection of 5-methyl cytosine and quantitation of its ratio to cytosine in DNA. Tenfold improvement in sensitivity over that obtained by conventional techniques was achieved (*P22*). Identification and quantitative determination of 5-methylcytosine can also be reached using a high-resolution mass spectrometer coupled with time averaging computer (*P10*). Mass spectra of analogues of some nucleic bases, e.g., 2-alkylthiouracils (*P25*), hydroxyalkyl inosines (*P11*), and 8-azapurines (*P3*), were reported. Various methods of identification of cytokinines using GC/EI MS (*P5*, *P8*, *P13*) or GC/CI MS (*P6*) have been described.

The structure of a highly modified nucleoside--N/(9-β-D-ribofuranosyl-2-methylthiopurin-6-yl)-carbomoyl/threonine--from mammalian transfer RNA was elucidated by high resolution mass spectrometry on 35 μg of material using methylated, deuteromethylated, trimethylsilylated, and deuterotrimethylsilylated derivatives (*P26*). A mass spectrometric method for the quantitation of the percentages of deoxyadenosine, deoxyguanosine, deoxycytidine, and thymidine in intact DNA molecules was devised (*P14*). The mass spectra of the permethyl derivatives of apiosyl nucleosides were detected and compared with those of their ribosyl analogues (*P23*). The EI mass spectra of O^6,5′- and O^2,2′-anhydrouridine were examined as models for the fragmentation behavior of pyrimidine anhydronucleosides (*P18*). *tert*-Butyldimethylsilyl, cyclotetramethyleneisopropylsilyl, and cyclotetramethylene-*tert*-butylsilyl derivatives of nucleosides were prepared and studied by GC/MS. The valuable features of the derivatives include better separation by GC and improved structural information by EI MS compared to trimethylsilyl derivatives (*P19*). The procedure for permethylation of nucleosides suitable for both GC/MS and preparative scale reactions was presented (*P16*). Mass spectra of model monobenzylated nucleosides (*P7*) and some other modified nucleosides (*P1*) were studied using low and high resolution mass spectrometers. FD MS was applied to the study of nucleoside antibiotics (*P9*). In the FD mass spectra of cordycepin, tubercidin, formicin, showdomycin, and some other antibiotics, $M^{+\cdot}$ or MH^+ ion was usually present as base peak. In C-nucleosides, only $M^{+\cdot}$ or MH^+ was observed at best anode temperature. The fragment ions due to the protonated base moiety of the molecules were observed as the most notable in many spectra.

The EI mass spectra of the trimethylsilyl derivatives of 3′- and 5′-monophosphoric acids of guanosine, uridine, cytidine, and adenosine were detected. In all cases the m/z 501 ion is far more abundant for the 3′-isomer than for the 5′-isomer (*P4*). 3,N^4-Etheno-*O*-trimethylsilyl derivatives of nucleosides and nucleotides of cytosine were studied as derivatives for GC and mass spectrometry; ethenylation blocks further derivatization of the base and therefore precludes chromatographic problems associated with trimethylsilylation at position N^4 of cytosine (*P21*). The mixed derivatives exhibit satisfactory GC properties and produce $M^{+\cdot}$ ions of greater abundance than in the case of the corresponding trimethylsilyl derivatives. Nucleotides prepared by methylation of 5′-UMP, 5′-TMP, 5′-, 2′-, and 3′-AMP, respectively, with trimethylanilinium hydroxide, were analyzed by mass spectrometry (*P17*). The analysis of methylation products of ApA, UpU, ApU, UpA by FD mass spectrometry has been reported; both the relative amounts of the various methylation products and the sites of methylation could be detected (*P15*). A mass spectrometric method was devised for the analysis of reaction products containing protecting groups at any stage in the chemical synthesis of oligodeoxyribonucleotides (*P2*).

Intact DNA and RNA were studied by pyrolysis mass spectrometry. A review concerning this topic was presented by Wiebers (*P24*). Pyrolysis of underivatized homogeneous oligoribonucleotides in the source of a mass spectrometer leads to production of simple mass spectra which resemble the spectra of the bases themselves. It is proposed that pyrolysis occurs by H transfer to the base moiety followed by elimination of the neutral base. Ionization by EI gives rise to the observed spectra. Mixed oligoribonucleotides pyrolyze readily to give spectra of adenine and uracil, but evidence for the presence of guanine and cytosine in mixed polymers and native RNAs is difficult to obtain, presumably because of their low vapor pressure. The method may be useful for detection of modified bases in *t*-RNA and for studies of temperature effects on RNA pyrolysis (*P12*).

Carbohydrates. A review with 268 references on mass spectrometry of carbohydrates has been published in Russian (*Q11*). Trimethylsilyl ethers of methoximes were used for GC/MS analysis of monosaccharides in human seminal plasma (*Q58*) and alduloses produced by irradiation of carbohydrates (*Q12*). The CI mass spectra of peracetylated aldononitriles of rhamnose, fucose, arabinose, xylose, ribose, mannose, glucose, galactose, some glucose methyl ethers (*Q32*), and aldoses containing acetamido, amino, deoxy, and thio substituents have been presented. Chemical ionization mass spectra indicated the molecular masses of the derivatives and the number of aldehyde and alcohol groups in the parent aldose (*Q54*). Peracetates of aldononitriles were employed for mass spectrometric identification of methylated monosaccharides obtained from some unusual dextranes (*Q53*).

GLC and EI mass spectra of trimethylsilyl and trimethylsilylated butaneboronate derivatives of polyhydroxyalkyl pyrazines have been reported (*Q60*). Rao and Roy described the preparation and mass spectra of some partially methylated alditol acetates from D-galactose (*Q45*). Mass spectrometric analysis of alditol derivatives proved to be helpful in elucidation of structure of the new monosaccharide in the *Vibrio cholerae* O-antigen (*Q27*) and in identification of the *N*-glycolylneuraminyl-(2→8)-*N*-glycolyl-neuraminyl group in a trout egg glycoprotein (*Q17*).

Underivatized D-glucose, D-ribose, D-mannose, D-galactose, and L-sorbose were distinguished by collisional activation spectra of the corresponding ions formed by Li^+, Na^+, and K^+ ion attachment under FD conditions (*Q47*). Ott et al. prepared selectively deuterated permethyl ethers of arabinopyranose, gluco-, and galactopyranose; examination of the mass spectra of these compounds allowed the partial revision of previously proposed fragmentation schemes (*Q41*, *Q42*). New data on the fragmentation of methyl 2,3,4,6-tetra-*O*-methyl-β-D-galactopyranoside under CI were obtained (*Q23*). The mass spectrometric method of identification of partially methylated methyl pentopyranosides has been developed (*Q35*). The fragmentation of methyl 2,3,5,6-tetra-*O*-methyl-D-glucofuranoside under EI is described using data for labeled analogues and metastable measurements (*Q22*). The mass spectra of negative ions of methyl ethers of glycopyranosides were demonstrated to be insensitive to stereochemical effects (*Q4*). A standardized method for the investigation of trimethylsilyl sugars is described (*Q18*). Trimethylsilyl derivatives were used for GLC-mass spectrometric examination of 3-ketoses and 2-heptuloses (*Q39*). The trimethylsilyl ethers of D-glucose, D-galactose, and D-mannose were analyzed by GLC/CIMS with ammonia or isobutane as reagent gas. MH^+-ions were detected. The CI mass spectra are sensitive to configuration and ring size (*Q37*). Mass spectral analysis of methyl α-D-glucopyranoside trimethylsilyl derivatives (containing *O*-palmitoyl at C2, C3, C4 or C6) and of corresponding deuterated derivatives was used to detect the position of the fatty acid moiety (*Q43*).

The new multistep hydrogen rearrangement was found (*Q44*): methyl 2,3,4-tri-*O*-acetyl-6-*O*-palmitoyl-α-D-glucoside fragmented under EI with loss of MeOH by intramolecular hydrogen transfer from the palmitoyl aliphatic chain to the palmitoyl carbonyl oxygen, followed by hydrogen migration from $C{=}OH^+$ to the glucosidic methoxyl group. The MeOH elimination reaction is important for 6-*O*-valerates and higher homologues. Mass spectrometry was applied for locating sulfate groups in monosaccharide sulfates (*Q24*). The structures of some rearrangement ions in the EI induced fragmentation of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside and phenyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-glucopyranoside have been investigated using high resolution, deuterium labeling and linked scan (B,E) techniques (*Q31*). The mass spectra of phosphite triesters of methyl α-D- and methyl β-D-ribopyranoside have been demonstrated to be markedly different (*Q5*). Mass spectra of 1,5-anhydro-D-xylitol acetyl derivatives (*Q59*) and 2,3-epithio-D-allose (*Q62*) were reported.

Mass spectrometric fragmentation pathways of the *O*-trimethylsilyl derivatives of hexuronic acids and their lactones were studied and specific effects of the carboxyl group upon the fragmentation patterns were revealed (*Q28*); the lactones produced less complex spectra with the base peak at m/z 230. The EI mass spectra of *O*-methylglucopyranosiduronamids (*Q34*) and *O*-trimethylsilyl aniline glucuronides were also published (*Q3*). Small amounts of pyridine injected into the batch inlet of the mass spectrometer and used concurrently with ammonia or isobutane under normal CI conditions were shown to provide an effective system for the characterization of trimethylsilyl derivatives of glucuronides by CI mass spectrometry; using this technique, little fragmentation of the glucuronide occurred and addition of a protonated pyridine species to the intact glucuronide provided an intense signal at m/z = (M + 80).

In-beam mass spectra were obtained for 11 amino sugars; most compounds exhibited an M + H peak and the spectral features are a combination of those of the conventional EI mass spectra and some major peaks originating from the M + H ions (*Q38*). The *N*-(3-hydroxytetradecanoyl) derivatives of 2-amino-2-deoxy-D-glucose, 3-amino-3-deoxy-D-glucose, and 6-amino-6-deoxy-D-glucose were prepared and mass spectra of trimethylsilyl ethers were examined (*Q10*). The mass spectra can be used to detect the location of the *N*-acyl chain on the aminoglucose residue. Trimethylsilyl ethers of *N*-acetyl amino sugars from bacterial lipopolysaccharides were identified using GC/EI and CI mass spectrometry: *N*-acetylglucosamine and *N*-acetylgalactosamine were distinguished by their EI mass spectra; CI enabled distinction of *N*-acetylglucosamine and *N*-acetylmannosamine from *N*-acetylgalactosamine and *N*-acetylquinovosamine, and *N*-acetylglucosamine from *N*-acetylmannosamine (*Q9*).

General methods were described for the spectrometric and GC analysis of neuraminic acid derivatives; mass spectra and GC data were tabulated for numerous natural and synthetic sialic acid derivatives (*Q25*). Sialic acids were analyzed by mass spectrometry after conversion into peracetylated methyl esters of 5-acylamino-3,5-dideoxynononic acids (*Q55*) or partially *O*-methylated derivatives of methyl *N*-acetyl-*N*-methyl-β-D-neuraminate methyl glycoside (*Q61*). Neuraminidase-susceptible and total *N*-acetylneuraminic acid in cells was determined by selected ion monitoring (*Q46*).

Structural determination of various glycosides including *C*- and *O*-glycosylflavones and flavanones (*Q8*, *Q48*), ginsengoside Rg_2 (*Q57*), oleuropein and ligustroside (*Q52*), steroid and triterpene saponines (*Q50*), and pennogenin and hederagenin glycosides (*Q51*) was done using EI (*Q8*, *Q48*, *Q52*, *Q57*) or FD (*Q50–Q52*) mass spectrometry. Some *N*-glycosides as 5,5-diphenylhydantoin glucuronide (*Q56*) and 4-*N*-2-acetamido-2-deoxy-D-glucopyranosyl-L-asparagine (*Q33*) were characterized by means of EI mass spectra.

To record mass spectra of underivatized oligosaccharides, new mass spectrometric methods were developed. W. R. Anderson and co-workers applied in-beam technique to obtain EI mass spectra of some unprotected disaccharides (*Q1*). A. K. Ganguly et al. (*Q15*) demonstrated that negative chemical ionization with CF_2Cl_2 is a convenient mass spectral technique for structural studies of oligosaccharides (up to pentasaccharides). Oligosaccharides produced intense (M + Cl) ions and few fragment ions corresponding to the loss of one or two discrete sugar units from either end of the oligosaccharide chain. The marked difference in the mass spectra of methyl ethers and acetates of two isomeric D-ribofuranosylribitols isolated from capsular polysaccharides of *Haemophilus influenzae* type b and *Escherichia coli K 100* allowed clear distinction between 1- and 2-*O*-D-ribofuranosylribitol (*Q14*). The EI mass spectra of permethylated disaccharides with 1 → 1, 1 → 2, 1 → 3, 1 → 4, 1 → 5, and 1 → 6 glycosidic bonds are presented (*Q21*). The spectra allowed identification of the glycosidic bond position. GC/MS of oligosaccharide mixtures (as methylated alditols) with *N*-acetylhexosamines at the reducing ends was shown to permit detection of the monosaccharide units sequence and detection of the location of the glycosidic bonds between amino sugars and the preceding monosaccharide residue (*Q36*, *Q63*). Analysis of hexosaminitol-containing disaccharide alditols from rat brain glycoproteins and gangliosides as trimethylsilyl derivatives by GC/MS showed that *O*-glycosidically linked carbohydrate units of the glycoproteins contained two disaccharides: α-D-galactosyl 1 → 3-*N*-acetyl-D-galactosaminitol and β-D-galactosyl 1 → 3-*N*-acetyl-D-galactosaminitol, whereas only the latter was obtained from the gangliosides (*Q13*). The EI mass spectrum of octa-*O*-trimethylsilylsucrose was discussed (*Q6*). Fragmentation of some disaccharides was examined using carbon-13 labeling (*Q7*). Mass spectrometry was also applied for characterization of the fluorescent 2-aminopyridine derivatives of oligosaccharides (*Q16*), oligosaccharides from sphingoglycolipids (*Q2*) and human transferrin (*Q26*), partially *N*-acetylated derivatives of kanamycin A (*Q20*), flambamycin and its degradation products (*Q40*), aldobiuronic, pseudoaldobiuronic acids (*Q29*), and some other acidic disaccharides (*Q30*).

Curie point pyrolysis and field ionization mass spectrometry were used with moderate success for structural analysis of some polysaccharides (*Q49*).

Complex Lipids. Mass spectrometry of various types was discussed in several reviews (*R13*, *R14*, *R17*). Applications of combination of liquid chromatography with mass spectrometry (LC/MS) to lipid analysis have been considered by Privett and Erdahl (*R19*). The sensitivity of the LC/MS system was 1 ng per component separated in the eluate of a

high efficiency column, and capabilities of the system were demonstrated by its application to triglycerides, glyceryl ethers, glyceryl diesters, glycerophosphatides, and sphingolipids. Efficiency of soft ionization (CI, FI, and FD) mass spectral methods for lipid analysis was discussed by Games (*R9*).

Ariga and co-workers (*R1*) proposed the method of determination of double bond positions in polyunsaturated fatty acid methyl esters by GC/CI mass spectrometry. Negative ion mass spectrometry was employed for analysis of fatty acid mixtures without preliminary separation (*R12*); the fatty acids were esterified with *p*-nitrobenzylbromide, the mass spectra of the esters contained practically only carboxylate anions thus allowing direct analysis of the mixtures.

The analysis was reported of 1,2-dihexadecyl and 1,3-dihexadecylglycerols by GC and mass spectrometry of their trimethylsilyl derivatives (*R21*); the mass spectral identification of 1,2-dihexadecyl-, 1-hexadec-1-enyl-2-hexadecanoyl-, 1-hexadecyl-2-hexadecanoyl-, and 1,2-dihexadecanoylglycerol was also discussed. Microdetermination of molecular species of oligo- and polyunsaturated diacylglycerols by GC mass spectrometry of their *tert*-butyldimethylsilyl ethers was described (*R16*). Batrakov et al. (*R2–R4*) used mass spectra of metastable ions (DADI and defocusing techniques) for characterization of molecular species of triglycerides (*R2*), glycerophospholipids (*R3*), and microbial lipoaminoacids (*R4*). The mass spectra of monoacyl-*sn*-glycerol carbonates were shown to exhibit M^+ ions and acyl cations of high intensity; the dioxolan-2-one ring was remarkably stable to EI (*R18*).

Aldehydrogenic phospholipids were examined by means of FD mass spectrometry (*R6*). Phosphoserine and phosphothreonine trimethylsilyl derivatives showed good GC-mass spectral properties, their mass spectra being readily applicable for identification of these two compounds; the high abundance of several phosphorus-containing rearrangement ions is remarkable (*R22*). The potential value of open-tubular GC/MS as a rapid procedure for the concurrent analysis of the major classes of polar lipids after enzymatic dephosphorylation was demonstrated by Gaskell and Brooks (*R10*).

The EI mass spectrum of an ornitine-containing lipid from *Thiobacillus thiooxidans* was interpreted using exact mass measurements, low and high energy ionization, and defocused metastable studies (*R11*).

Submicrogram quantities of trimethylsilyl derivatives of cerebrosides were analyzed by direct probe inlet CI MS with isobutane as reagent gas (*R15*). It was shown that useful structural information can be obtained and molecular species can be detected this way. Further examples of successful application of EI mass spectrometry to characterization of various glycosphingolipids were published (*R5, R7, R8*). The FD spectra of several diacyltrehaloses were presented using cationization by CsI (*R20*). The synthetic cord factor (dimycoloyl trehalose) containing 100 carbon atoms produced an intense peak at the expected m/z value for the $(M + Cs)^+$ ions.

BIOMEDICAL APPLICATIONS

Applications of mass spectrometry in biomedical research have continued to expand at a dramatic pace over the past two years. GC/MS remains the single most widely used technique in this field, although significant advances have been made in the development and application of "soft" ionization methods for the study of polar and/or thermally-labile compounds which are not amenable to analysis by GLC. The volume of literature on biomedical applications of mass spectrometry published during the present review period is so large that a comprehensive discussion of the topic would be impossible. Considerable selection of material has therefore been necessary in an effort to highlight the more important developments and novel applications of mass spectrometry in this field. The following section of the review has been subdivided into applications in the general areas of Pharmacology and Toxicology, Biochemistry, and Clinical Chemistry. While the borderlines between these disciplines are often ill-defined, the section on Clinical Chemistry has been confined to applications of mass spectrometry in investigations performed in human subjects or to the analysis of endogenous constituents of human physiological fluids. Important areas of biomedical research which have not been covered in this review include food science and the study of volatile constituents of human body fluids; however, surveys of the role of mass spectrometry in each of these areas have been published recently (*B15, B35, B37*).

PHARMACOLOGY AND TOXICOLOGY

Mass spectrometry continues to play an increasingly important role in studies in pharmacology and toxicology. In addition to being widely employed for the structural elucidation of drug and other xenobiotic metabolites, MS techniques in general, and GC/MS methods in particular, are being used extensively for quantitative applications in this field. Indeed, the growing requirement for accurate quantitative determinations of low levels in biological fluids of both endogenous and xenobiotic substances has served as a major stimulus for the development of highly sensitive and specific quantitative MS methodology. Consequently, qualitative and quantitative applications are discussed separately in this section. The use of stable isotope labeling techniques, in conjunction with MS, is expanding rapidly and some of the more novel applications of stable-isotope-labeled compounds to problems in pharmacology and toxicology are reviewed in a separate sub-section.

Qualitative Applications. In general, EIMS techniques predominate in this area, although CIMS is frequently the ionization method of choice for rapid "screening" of extracts of blood or urine for the presence of known drugs and their metabolites (*S14*). Although GC/MS techniques are frequently employed for this purpose, direct insertion CIMS has been shown to be a valuable, and in some cases preferable, alternative. Thus, a rapid procedure for the screening of urine samples for the presence of 14 basic drugs, based on direct insertion CIMS with isobutane as reagent gas, has been adopted by the New Jersey State Police for forensic applications (*S71*). Studies on the metabolism of thermally labile compounds have also benefited from the use of direct insertion CIMS; in an investigation of the metabolic fate of procarbazine, an anti-tumor agent, a series of chemically unstable intermediates was isolated by HPLC and successfully characterized by direct insertion CIMS (*S92*). GC/CIMS has been used to identify a series of phthalate esters whose EI mass spectra are frequently dominated by the structurally uninformative m/z 149 ($C_8H_5O_3^+$) fragment ion (*S1*). Reports on the use of GC/CIMS alone in drug metabolism studies are relatively rare, although Thomas and co-workers have described the identification of eight hydroxylated metabolites of etidocaine by this technique (*S91*). Negative ion CIMS, which has been applied by Ryhage, Brandenburger, and coworkers to the identification of a number of hypnotic agents (*S21*) and amphetamine congeners (*S50*), would appear to be a valuable complementary ionization technique to EI and positive ion CI for many pharmacological and toxicological applications (*S10*). Dougherty and co-workers have applied negative ion CIMS to detect a variety of environmental pollutants in samples of human adipose tissue and seminal fluid (*S45*). Other "soft" ionization techniques, notably field desorption and "in-beam" chemical ionization, are proving to be of great value in the characterization of polar drug conjugates and covalent adducts, as discussed below.

The most rapidly developing MS technique in studies of drug metabolism, however, is repetitive scanning GC/MS under computer control. By this approach, repeated analyses of stored data may be carried out via the data system, "mass chromatography" being the most popular technique for the detection of drug metabolites present as minor components in complex biological extracts. An example of the application of this approach for the identification of metabolites of 3-phenylpropyl carbamate in rat urine and feces is given in a paper by Horie and Baba (*S35*).

The formation of reactive (and hence potentially toxic) intermediates of metabolism continues to receive widespread attention. Despite numerous studies on the metabolism of the analgesic agent acetaminophen (paracetamol), the identity of the reactive electrophilic species believed to be responsible for the hepatic and renal damage associated with massive overdose of this drug has not yet been established. By means of HPLC and GC/EIMS techniques, Hinson et al. identified *N*-hydroxyacetaminophen as a microsomal metabolite of *N*-hydroxyphenacetin but apparently not of acetaminophen (*S31*). In view of the recognized toxicity of a number of

hydroxylamines, reports (*S80–S82*) of the urinary excretion in man of major quantities of *N*-hydroxylated products of barbiturate metabolism have been of some concern. With the aid of synthetic reference *N*-hydroxy barbiturates, however, Gilbert and co-workers employed GC/CIMS to show that *N*-hydroxylation was not, in fact, a major pathway in the metabolism of either aprobarbital (*S26*) or amobarbital (*S25*) in humans. This finding was substantiated by Tang et al. who reported that the metabolites of amobarbital and phenobarbital previously claimed to be *N*-hydroxylated derivatives were actually *N*-glucoside conjugates, the identification of which was achieved by a combination of techniques including methane CIMS (*S83, S84*). A further example of erroneous structural assignment involving *N*-oxidation has been reported for the products formed by chemical and metabolic oxidation of phenothiazine and 2-chlorophenothiazine, which have now been correctly characterized as 7-hydroxyphenothiazines, phenothiazin-3-ones, and phenothiazin-7-ones (*S6*).

Several papers detail the use of mass spectrometry for the identification of epoxides and/or related dihydrodiol metabolites, including those derived from hexobarbital (*S90*), 3-methylcholanthrene (*S42*), 8-methylbenz[*a*]anthracene (*S93*) and 7,12-dimethylbenz[*a*]anthracene (*S15*). In a re-investigation of the biological fate of naphthalene in the rat, evidence was obtained by M. G. Horning and co-workers for the involvement of a number of epoxides and endoperoxides, in addition to 1,2-naphthalene oxide, as metabolic intermediates (*S36*). Furthermore, the GC and GC/MS properties of several urinary metabolites identified in this study indicated that *anti*-1,2:3,4-naphthalene dioxide may be formed in vivo. Recent studies on the metabolism in several species of the skeletal muscle relaxant cyclobenzaprine have led to the identification of two new dihydrodiol metabolites (1,2- and 10,11-dihydrodiol), in addition to the previously described 10,11-epoxide (*S37, S38*). An investigation by GC/MS of the pattern of urinary metabolites of diethylstilbesterol (DES) in the fetal, neonatal, and adult mouse has indicated that β-dienestrol does not appear to be formed through a DES epoxide (*S52*). Stereochemical aspects of dihydrodiol formation are frequently studied by determining whether the diol of interest can be converted to a cyclic derivative, e.g., acetonide or boronate ester, a reaction considered to be characteristic of *cis*-diol functionalities. It is of interest to note, therefore, that some metabolic *trans*-dihydrodiols can react with methaneboronic acid to yield the corresponding methylboronate esters (*S12*). Although widely used for several years in the GC/MS analysis of carbohydrates, steroids, and prostaglandins, cyclic boronates are now finding application in the field of drug metabolism as exemplified by studies on the β-adrenoceptor antagonist alprenolol (*S32–S34*) and the anti-protozoal agent MK-436 (*S88*).

Recent investigations on the metabolism of a variety of aromatic hydrocarbons, including several halogenated derivatives, have revealed the formation of sulfur-containing metabolites which are frequently thiomethyl derivatives. GC/MS has been employed to characterize thiomethyl metabolites of naphthalene (*S76*), biphenyl (*S29*), bromobenzene (*S55*), hexachlorobenzene (*S39, S43*), tetrachlorophenols (*S2*), pentachlorophenols (*S3*), 2,4,2′,4′-tetrachlorobiphenyl (*S54*), polychlorinated dibenzo-*p*-dioxins (*S86*) and the pesticide chlorpyrifos (*S48*). In a study of the origin of the *S*-methyl group in methylthio metabolites of naphthalene, Stillwell et al. (*S75*) employed an in vivo deuterium labeling technique in which rats were first maintained on a methionine-free diet, after which their diet was supplemented with L-[$^2H_3$]-methionine. Following administration of naphthalene, urinary metabolites were isolated and analyzed by GC/MS which indicated that the methylthio-containing compounds had incorporated the deuterium label. This study thus showed that the methyl group attached to sulfur in these metabolites was derived from methionine. In a study of the metabolic fate in dogs of a mixture of polybrominated biphenyls, 6-hydroxy-2,4,5,2′,4′,5′-hexabromobiphenyl was isolated from feces and characterized by MS and NMR; interestingly, this metabolite was found to undergo intramolecular dehydrobromination on GC analysis to give two isomeric pentabromodibenzofurans which were identified by GC/MS (*S23*).

Pohl and co-workers (*S67*) have applied MS to a study of the mechanism by which the antibiotic chloramphenicol (CAP) is metabolized to a chemically reactive intermediate; a new metabolite, which was formed in incubations with rat liver microsomes, was identified using direct insertion CIMS as the oxamic acid derivative of the parent drug. Formation of this compound in vitro supports the contention that CAP is metabolically activated to an oxamyl chloride reactive intermediate which either hydrolyzes to the oxamic acid or acylates protein. GC/MS techniques have been employed in a number of studies on the metabolism of hydralazine, a potent anti-hypertensive drug whose use is associated with certain toxic side-effects (*S28, S58, S85*). In two of these studies (*S58, S85*), hydrazine has been identified as a urinary metabolite of the drug in animals and humans, respectively. Evidence that a reductive pathway may be important in the generation of toxic metabolites of nitrosamines has been presented by Gal, Estin, and Moon (*S22*), who employed GC/MS to identify bibenzyl as an in vitro metabolite of *N*-nitrosodibenzylamine; this biotransformation is proposed to result from a two-electron reduction of the substrate to 1-hydroxy-2,2-dibenzylhydrazine, an unstable compound which breaks down to bibenzyl and nitrogen. Concern over the possible toxicity of phthalate esters, used extensively as plasticizers and present as environmental contaminants, has led to studies on their metabolism in vivo (*S17*). The concentrations of various phthalate contaminants in intravenous solutions stored in PVC bags has been determined by GC/MS employing single ion monitoring of the characteristic fragment ion at m/z 149 (*S87*). Further applications of GC/MS to toxicological problems include the identification of a methylated catechol metabolite of glutethimide isolated from biological fluids of overdose victims (*S54*) and the detection of the mutagenic metabolite, 2,3-dibromopropanol, in the urine of children wearing sleepwear which had been treated with the flame retardant tris(2,3-dibromopropyl)phosphate (*S9*); in the latter example, negative ion MS was employed for detection of the metabolite, using either CI or API techniques.

McMahon et al. have applied GC/MS to study the biotransformation of 4′-ethynyl-2-fluorobiphenyl in the rat, when evidence was obtained for the formation of a highly reactive intermediate, 2-fluoro-4′-biphenylketene (*S79*). A further paper from the Lilly group reports on the metabolism in the rat of the hydrocarbon isopropylbiphenyl; biphenylpropionic acid, an anti-inflammatory agent, was shown by GC/MS to be the principal metabolite in plasma, thus explaining the anti-inflammatory action of the parent compound (*S78*). Novel routes of biotransformation which have been detected by MS include hydroxylation α to an acetylenic group in oxotremorine (*S47*) and oxidative deesterification of an isopropyl ester, flamprop-isopropyl (*S57*). Studies on the metabolism of synthetic steroids by MS are relatively rare, although Chu et al. report on the use of direct insertion methane CI to characterize 6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione as a major urinary metabolite in the rhesus monkey of the corticosteroid flusinolide; formation of this metabolite is of interest from a mechanistic standpoint in that concomitant loss of a 6α-F substituent is involved (*S16*). Medroxyprogesterone acetate has been shown to undergo bacterial ring-A reduction, despite the fact that it carries substituents at both 6α and 17α, positions which are known to inhibit reduction of the 3-oxo-4-ene grouping (*S51*). Human metabolites of the antidepressive agent amitriptylinoxide have been detected in plasma by employing selected ion monitoring GC/MS of the species formed via Cope elimination of the parent *N*-oxides (*S53*), while metabolites in man of the monoamine oxidase inhibitors pargyline and deprenyl have been characterized as *N*-methyl-benzylamine (*S66*) and amphetamine (*S70*), respectively. A comprehensive investigation of the biological fate of cambendazole, a broad-spectrum anthelmintic compound, has led to the identification of 14 urinary metabolites in cattle, swine, and sheep, and has shown that the thiazole ring is the major site of metabolic attack (*S89*). Finally, in studies on the metabolism of ibuprofen in human subjects, Jellum and co-workers report on the suitability of dialysis fluid as a medium for such work (*S65*).

The trend, noted in the previous review of this series (*S13*), toward the use of MS for the identification of drug conjugates as the intact species (rather than as the corresponding "free" metabolites liberated by enzymic hydrolysis) has continued over the past two years. A number of glucuronides have been isolated and characterized (following conversion to permethyl, per-TMS or methyl ester/TMS ether derivatives) by EIMS

using either direct insertion or GC/MS techniques. These include the *O*-glucuronides of oxaprozin metabolites (*S40*), procaterol (*S74*), 4-hydroxy-antipyrine (*S95*), 3-hydroxymethyl-antipyrine (*S95*) *N*-desmethyl-antipyrine (*S30*) and carbamazepine metabolites (*S49*), the *N*-glucuronides of anthranilate derived from diazonium cleavage of bilirubin-XIa glucuronide (*S18*), carbamazepine *N*-glucuronide (*S49*), and the *O*- and *S*-glucuronide conjugates of terbutryn (*S46*). Two novel types of *O*-glucuronide have been reported recently. The first of these was observed in a study of the metabolism of clofibrate, a hypolipidemic drug, which is rapidly hydrolyzed in vivo to give *p*-chlorophenoxyisobutyric acid (CPIB) which, in turn, undergoes conjugation with glucuronic acid. The glucuronide conjugate of CPIB was found to exist in two discrete forms, in one of which the glucuronic acid moiety possessed the normal β-pyranose structure while in the other it was present as the corresponding furanose ring system (*S30a*). In the second example, carazolol, a new β-blocking drug, was also found to give rise to two different types of glucuronide conjugate; in this case, MS indicated that these species corresponded to the expected *O*-glucuronide and to a novel bis-*O*-glucuronide in which two molecules of glucuronic acid were attached to one another via a C-1 → C-4 linkage (*S73*). Ionization techniques other than EIMS have been applied to the study of glucuronides, e.g., "in-beam" CIMS (*S19*).

Sulfate esters often present severe difficulties from an analytical point of view due mainly to their highly polar nature. In a study of the metabolism of trimethoprim in goats and pigs, for example, Nielsen and Dalgaard isolated from urine a sulfate conjugate which proved to be resistant to enzymatic hydrolysis by common forms of aryl sulfatase (*S57*). Analysis of the purified sulfate by high resolution EIMS gave a spectrum which was almost identical to that of the corresponding unconjugated metabolite, with the exception of an ion at m/z 63.964, due to SO_2^+. FDMS has been employed with some success in the characterization of sulfate esters, e.g., the sulfate of 9-hydroxyellipticine which yielded an $[M + H]^+$ ion (*S11*), although in other cases, e.g., the phenolic sulfate conjugate of *N*-hydroxyacetaminophen, no satisfactory results were obtained by this technique (*S24*). Approaches toward the derivatization of sulfates for MS analysis have included in situ methylation on the direct insertion probe using trimethylanilinium hydroxide (*S44*) and conversion to diesters, e.g., alkyl–aryl or diaryl sulfate esters (*S62*, *S63*). An alternative technique involves the direct conversion of phenolic sulfates to volatile derivatives of the parent phenols by reaction with an appropriate perfluroacid anhydride, followed by analysis of the products by GC/MS; in this approach, however, it is necessary to first remove unconjugated metabolites as these will also undergo derivatization with the acid anhydride (*S56*). Trimethylsilylation also appears to be an effective procedure for the direct conversion of phenolic sulfates to nonpolar derivatives; the conversion of morphine sulfate to morphine-TMS during treatment with *N*-trimethylsilylimidazole in pyridine serves to illustrate this reaction (*S94*).

Thioether conjugates (glutathione adducts, cysteine conjugates, and mercapturic acids) have received widespread attention since their formation in vivo usually reflects the production of a reactive metabolic intermediate. EIMS techniques have been of limited use in the analysis of glutathione conjugates, which are both very polar and thermally labile; fragment ions of low m/z are usually obtained from this class of compounds, as was the case with two isomeric glutathione conjugates of styrene oxide (*S61*). FDMS, however, has been applied with notable success to the characterization of a variety of glutathione derivatives, including the *S*-methyl, -ethyl, -isopropyl, -benzyl and -acetyl compounds (*S68*), and the glutathione conjugates of 2-hydroxy-estradiol (*S68*), *N*-methyl-4-aminoazobenzene (*S41*) and acetaminophen (*S5*). In the latter paper, collision-induced dissociation (CID) FDMS was employed to obtain structural information on both the acetaminophen glutathione and cysteine conjugates (*S5*). The glutathione adduct of acetaminophen has also been characterized (as its methyl ester) by use of "in-beam" CIMS techniques (*S77*). Cysteine conjugates can usually be rendered amenable to EIMS analysis by appropriate derivatization procedures, as illustrated in the case of 2-(*S*-cysteinyl)-*N*-isopropylacetanilide, a metabolite of popachlor in the rat, which was characterized by direct insertion EIMS as its *n*-butyl ester trifluoroacetamide derivative (*S64*). Mercapturic acids (*N*-acetyl cysteine derivatives) are usually analyzed by EIMS following esterification, an example of which is described by Reickert et al. who report on the identification of a mercapturic acid metabolite of 1,1-dichloroethylene in the rat (*S69*).

In a series of investigations by Ortiz de Montellano and co-workers into the mechanism by which certain compounds possessing terminal olefinic or acetylenic structures destroy cytochrome P-450 both in vitro and in vivo, "green" pigments have been isolated from liver and characterized as modified porphyrins by chromatographic and spectroscopic techniques. The abnormal porphyrins isolated from incubations of rat liver microsomes with 2-isopropyl-4-pentenamide (*S59*) and by treatment of rats with norethisterone (*S60*) have been analyzed, following esterification, by FDMS. The results of these studies showed clearly that the "green" pigments represented covalent adducts formed between the substrate and protoporphyrin IX in a 1:1 ratio, with the additional incorporation of one atom of oxygen, and indicated that the mechanism of P-450 destruction by these agents centers on the formation of reactive intermediates of metabolism which become covalently bound to prosthetic heme.

FDMS continues to play an important role in studies of the covalent modification of nucleic acids by alkylating or arylating agents. A cross-linked dinucleoside, 1,2-(diguanosin-7-yl)-ethane, has been isolated from the reaction of guanosine with the anti-tumor agent BCNU and analyzed by FDMS (*S27*). The principal aflatoxin B_1-DNA adduct formed in vivo in rat liver has been identified as 2,3-dihydro-2-(N^7-guanyl)-3-hydroxy-aflatoxin B_1 by chromatographic, spectroscopic, and FDMS methods (*S20*). Two recent investigations of the covalent binding of carcinogens to DNA by Kadlubar and coworkers have resulted in the identification of three nucleoside–arylamine adducts from *N*-hydroxy-2-naphthylamine (*S40a*) and two from *N*-methyl-4-aminoazobenzene (*S8*); in these studies both FDMS and high resolution direct insertion EIMS (of the trimethylsilylated derivatives) were employed to characterize the modified nucleosides. Similar techniques were used by McCloskey et al. to identify the major adducts formed in vitro between the carcinogen *N*-acetoxy-4-acetamidostilbene and guanosine, cytidine, and adenosine (*S72*).

Quantitative Applications. In the majority of quantitative applications of mass spectrometry in pharmacology and toxicology, advantage is taken of the high sensitivity attainable by the use of selected ion monitoring (SIM) techniques. However, in cases where relatively large amounts of sample are available for analysis, repetitive scanning over the full or a narrow mass range has been employed; examples of this approach, which offers greater versatility than SIM (*T41*) are to be found in papers on the analysis of propranolol (*T54*), ketamine (*T4*) and their metabolites.

While EI remains the most frequently employed method of ionization, use of CIMS for quantitative applications in this subject area has increased notably over the present reporting period, with methane and isobutane being the most popular reagent gases, followed by ammonia. Justification for the selection of CI over EI techniques often appears to be based on the assumption that the former approach, which typically yields simplified mass spectra in which the base peak carries a high proportion of the total ion current, must necessarily offer greater sensitivity of detection; while this may be true in certain cases, comparisons of absolute sensitivities obtainable by the two ionization techniques are seldom reported. The importance of comparing, in this connection, the relative ionization efficiencies as well as the qualitative appearance of the mass spectra obtained by different methods of ionization has been emphasized recently by Foltz, who evaluated EI vs. CI (methane and methane/ammonia) for the analysis of methadone and methamphetamine (*T7*). In favorable cases the use of negative ion CIMS should prove to be extremely valuable for the quantitative analysis of drugs and their metabolites at very low levels in biological extracts; the potential of this technique has been demonstrated by Hunt and Crow (*T20*) using reference compounds, and recently by Garland and co-workers who reported detection limits for clonazepam and the prostaglandin analogue TM-PGE_2 of <100 pg mL^{-1} from a 5-mL sample of plasma and 200 pg mL^{-1} from a 1-mL sample of plasma, respectively (*T8*, *T37*). Ion-

ization techniques other than EI and CI have been employed for quantitative analyses in only a few cases. In a study of the comparative bioavailabilities of two commercial preparations of imipramine, Heck et al. used a combination of HPLC and direct insertion field ionization MS to quantify the drug in plasma (*T14*); the authors claimed that the sensitivity and precision of the assay were approximately an order of magnitude greater than attainable by published GC/MS techniques using SIM. The use of FDMS for quantitative purposes has been reported by Miyazaki et al. (*T38*) and Lehmann, Schulten, and Schroder (*T29*); using a multichannel analyzer, the latter group reported quantitation of choline and acetylcholine in the picogram range with a precision of ≤10%. Further quantitative applications of FDMS have been to the determination of thallium in brain tissue samples (*T48*) and cyclophosphamide metabolites in urine (*T6*, *T47*).

The GC inlet continues to be by far the most widely used system for sample introduction in quantitative applications in this subject area (*T34*), although direct insertion techniques (*T34*, *T35*) have been employed successfully by a number of workers, including Marshall, Petersen, and Vouros who reported a limit of detection of 50 pg for LSD by this approach (*T31*). Direct probe CIMS assays have been reported for the anti-tumor agent BCNU (*T30*, *T57*) and *N*-hydroxyamide metabolites of lidocaine (*T42*), while EIMS methods have been developed for metabolites of the anti-neoplastic drug cyclophosphamide (*T22*) and for mixtures of compounds commonly found in cold medicine and anticonvulsant preparations (*T51*).

The two types of internal standard commonly employed in assay procedures based on MS, viz a stable-isotope-labeled analogue and a structural analogue of the compound of interest, appear to be used almost equally in pharmacological applications (*T34*). GC/MS assays in which quantitation is achieved by reverse stable isotope dilution procedures, however, are generally considered to offer greater accuracy and precision, as was found to be the case in an assay for carprofen by GC/CIMS (*T18*). Examples of quantitative GC/MS methods employing stable-isotope-labeled internal standards include those for nicotine (*T13*), propranolol (*T55*, *T56*) baclofen (*T50*), norethindrone (*T2*), 1-α-acetylmethadol and its principal metabolites (*T22*), amitriptyline and its major metabolites (*T9*), berberine (*T39*), propantheline bromide (*T53*), and sulfadimethoxine (*T17*). In the great majority of cases, deuterium has been the stable isotope of choice for preparation of labeled internal standards because of its relatively low cost and its availability at high isotopic purity in a wide variety of reagents and organic compounds which thus facilitate its incorporation into drugs and their metabolites by synthesis. In a GC/CIMS assay for clonazepam and its 7-amino metabolite, however, Min et al. employed as internal standards analogues labeled with a single atom of ^{15}N (*T36*), while Horie and Baba have investigated the use of analogues labeled with one atom of ^{13}C for this purpose (*T19*). Oxygen-18 has not yet been widely used, although in their GC/negative ion CIMS assay for clonazepam, Garland et al. adopted a multiply labeled variant, [^{15}N, $^{18}O_2$]clonazepam, as internal standard (*T8*). Difficulties encountered in the development of stable isotope dilution assays for polychlorinated compounds, in which broad isotope clusters result from the presence in the unlabeled compound of ^{37}Cl at the level of its natural abundance (approximately 24%), have been resolved in the case of the toxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) by the preparation of an analogue highly enriched in ^{37}Cl and, in addition, labeled with deuterium, [$^2H_4$, $^{37}Cl_4$]TCDD (*T12*). By use of this species as internal standard, virtually no cross-contribution was observed in the channels corresponding to unlabeled and labeled TCDD during SIM GC/MS analyses of commercial samples of 2,4,5-trichlorophenoxyacetic acid and 2,4,5-trichlorophenol. Compounds labeled with radioisotopes have not proven popular for use as internal standards for the quantitation of drugs and their metabolites by MS techniques, in contrast to their application for this purpose in the steroid hormone field (*T27*). Although a tritiated derivative of etorphine (specific activity 41 Ci mmol^{-1}) was initially employed as an internal standard in a GC/MS assay for etorphine in urine (*T24*), its use was later abandoned in favor of a deuterium-labeled analogue (*T23*). A commentary on the uses and functions of deuterated analogues in quantitative mass spectrometry has been published (*T49*).

Structural analogues of the compound-of-interest have been employed as internal standards in GC/MS assays for a wide variety of compounds, including bromocriptine (*T26*), 5-fluoro-2,4-pyrimidinedione (*T32*), lidocaine and its deethylated metabolites (*T15*, *T25*), amphetamine (*T46*), lorazepam and oxazepam (*T16*), carbamazepine and carbamazepine-10,11-epoxide (*T44*), imipramine, desipramine, clomipramine, and *N*-desmethyl-clomipramine (*T1*), terbutaline (*T3*), nicotine (*T5*), virazole (*T45*), prednisone and prednisolone (*T33*), and haloperidol (*T40*).

A noticeable trend in the development of GC/MS assays over the past two years has been in the adoption of open-tubular glass capillary columns which offer several advantages over packed GC columns for quantitative as well as qualitative analysis of drugs and their metabolites (*T5*, *T7*, *T28*, *T37*). In a comparison of packed vs. capillary column GC/MS for the assay of 16α-cyano-3β-cyclopentyloxypregn-5-en-20-one, an experimental steroid drug, Gaskell, Brooks, and Matin noted a considerable improvement in base-line stability during SIM operation with a capillary column due to decreased column "bleed"; furthermore, the enhanced resolving power of the capillary column led to greater specificity of detection and improved peak height to peak area ratio (*T10*). An alternative approach to improving the specificity of detection in quantitative MS assays has been in the use of moderate to high mass spectrometric resolution; thus Gaskell et al. performed SIM GC/MS at a resolution of 8500 in an assay for the antiestrogenic agent tamoxifen in order to eliminate interference from components of the extract which co-eluted with the drug or its internal standard (*T11*). An assay for pentoxyfylline, a vasodilator, has also benefited from this technique (*T52*), which can be expected to become more widely employed with the increasing availability of double focusing mass spectrometers to groups engaged in pharmacological research. The development in recent years of improved isolation and purification procedures, many of which are based on HPLC techniques, has been of great importance in further enhancing the specificity of assays based on mass spectrometry. Amberlite XAD-2 and Poropak Q have been evaluated for the extraction of phenylalanine mustard from samples of human plasma prior to assay by GC/CIMS (*T43*), while lipophilic Sephadex gels, used for some time in the steroid and lipid fields, are now being adopted in analytical protocols for drugs and their metabolites (*T10*, *T11*).

Stable Isotopes. In addition to their continued widespread use in the preparation of internal standards for isotope dilution assay procedures, stable isotopes are being employed increasingly, in conjunction with MS, for a variety of applications in studies of drug metabolism, disposition and toxicity (*U9*, *U23*, *U33*). The isotope cluster, or "twin ion" technique is rapidly gaining popularity in investigations of drug metabolism; in this approach, use of an equimolar mixture of unlabeled and stable-isotope-labeled forms of the drug leads to the formation of metabolites whose mass spectra exhibit characteristic isotope clusters, thus facilitating their detection by MS. Examples of the application of this technique have been to studies of the metabolism of alprenolol (*S33*), 3-(2′,4′,5′-triethoxybenzoyl)propionic acid (*U19*, *U20*), propantheline bromide (*U35*), potassium canrenoate (*U34*), propranolol (*U28*), 1-butyryl-4-cinnamylpiperazine (*U24*), and 3-phenylpropyl carbamate (*U16*). In the case of the last compound cited, a comparison has been made of the use of an analogue of the drug labeled with five atoms of deuterium vs. a $^{13}C_1$ analogue for use in the isotope cluster technique (*S35*). It is of interest to note that the radioisotope ^{14}C has been employed for the first time in an isotope cluster study (*U7*).

Mechanistic aspects of drug metabolism have benefited greatly from the use of analogues labeled specifically with stable isotopes and sample analysis by MS. This is particularly true for studies on the relationship between metabolism and toxicity, as exemplified by work on the mechanism by which the antidepressant drug iproniazid produces liver injury (*U26*); the results of the investigation, which employed substrates labeled with both deuterium and radioactive isotopes, indicated that isopropylhydrazine is the metabolite of iproniazid which is oxidized by a microsomal cytochrome P-450 enzyme to a species which alkylates tissue macromolecules. Analogues of phenacetin, labeled specifically with ^{18}O or deuterium in the *p*-ethoxy group, have been employed by Nelson and coworkers to investigate arylating and alkylating pathways of

phenacetin metabolism (*U27*). The results of these studies indicated the operation of multiple pathways for reactive metabolite formation from phenacetin and showed that the major pathway in vitro is different from that in vivo. In a further examination of this problem, Hinson et al. again employed [*p*-^{18}O]phenacetin to demonstrate that, in hamsters, de-ethylation of phenacetin to acetaminophen, followed by activation of acetaminophen to a reactive electrophilic intermediate, is the predominant toxic pathway in vivo (*U15*). This conclusion is supported by the observation that [*p*-1,1-$^{2}H_2$]ethoxyacetanilide ([$^{2}H_2$]phenacetin), which is metabolized less rapidly to acetaminophen than its unlabeled counterpart, exhibits lower toxicity in hamsters than does phenacetin (*U25*). A combination of GC/CIMS and direct insertion EIMS methods was used in the above studies.

In a series of investigations on the metabolism of halocarbons to carbon monoxide, Anders et al. have employed GC/EIMS together with ^{18}O, ^{13}C, and ^{2}H labeling techniques to define the mechanisms of the reactions involved (*U2*, *U22*, *U32*). Formyl halides are indicated as intermediates in the metabolism of dihalomethanes while dihalocarbonyls, which may be trapped by reaction with cysteine, are formed from haloforms. In a related study, Pohl and co-workers have demonstrated the existence of a deuterium isotope effect in the in vivo bioactivation of chloroform to phosgene; the latter species was trapped by reaction with cysteine and characterized as the methyl 2-oxothiazolidine-4-carboxylate by GC/EIMS (*U31*). Studies on the metabolism in vivo of the sensory irritant dibenz[*b*,*f*]-1,4-oxazepine have shown that formation of the corresponding 7-hydroxy derivative occurs via an intermediate arene oxide, as evidenced by the NIH shift which occurs on metabolism of the [7-^{2}H] analogue (*U11*). GC/MS methods have been used to reveal a deuterium isotope effect in the hydroxylation of biphenyl at C-3, but not at positions 2 or 4, suggesting that different mechanisms are involved; furthermore, studies with ^{18}O suggested that formation of the catechol metabolite, 3,4-dihydroxybiphenyl, takes place via two consecutive hydroxylations (*U6*). The metabolism of nicotine by rabbit liver microsomal fractions in the presence of NaCN has been carried out in an attempt to trap reactive *N*-methyliminium species during the course of oxidative demethylation; using specific deuterium labeling techniques, two isomeric cyanonicotine compounds were isolated and characterized by GC/EIMS (*U29*).

Multiple labeling with ^{2}H and ^{13}C, in conjunction with GC/MS, has been employed by Baillie et al. in a study of qualitative, quantitative, and mechanistic aspects of clonidine metabolism (*U5*), while deuterium-labeled variants of the organophosphorus drug, metrifonate, were used to demonstrate the nonenzymatic conversion of this compound into dichlorvos, a direct-acting cholinesterase inhibitor (*U30*). Following co-administration of chloral hydrate and [$^{2}H_6$]-ethanol to a rat, Wong and Biemann used GC/MS to identify 1-deutero-2,2,2-trichloroethanol as a urinary metabolite; this finding thus confirmed an earlier hypothesis that the synergistic effect of chloral hydrate and ethanol is due to their coupled redox reaction in the alcohol dehydrogenase-mediated enzymatic process (*U39*). Further examples of the use of MS and stable isotopes for mechanistic studies of enzymatic action have been in investigations of regioselectivity in the hydration of *cis*-1,2-disubstituted epoxides (*U10*) and of conjugation and hydrolysis of isoborneol glucuronide (*U18*), ^{18}O being the tracer species used in each case. The combined use of ^{13}C NMR and MS techniques for the identification of metabolites of specifically ^{13}C-labeled substrates has been described by Wiebe et al. (*U37*) and by Hawkins and Midgley (*U12*).

Specialized applications of stable-isotope-labeling which may be expected to find wider application in the near future include studies on the pharmacokinetics of drugs under steady state conditions (*U3*), comparisons of the bioavailability of different formulations (or routes of administration) of the same drug (*U1*, *U13*, *U14*, *U38*), and studies on stereoselective aspects of drug disposition (*U8*, *U17*, *U21*, *U36*). A novel use of deuterium labeling has been in a study of the effect of a drug on its own metabolism, as applied to an investigation of the biological fate of the analgesic agent 1-butyryl-4-cinnamylpiperazine in the rat during the development of tolerance to the drug (*U4*). Each of these areas of application holds particular promise for use in human subjects, where safety considerations severely restrict the use of radioactive isotopes.

BIOCHEMISTRY

Sterols, Steroids, and Bile Acids. Selected aspects of the use of mass spectrometry in research on steroids have been reviewed recently by Brooks, who emphasizes the value of GC/MS techniques, used in conjunction with appropriate derivatization procedures, for the characterization of complex mixtures of sterols and steroid hormones (*V8*). Although EI ionization is employed in the vast majority of applications in this field, CI has proven useful in certain situations, as exemplified in preliminary studies on the direct identification of individual steroids in biological matrices through analysis of their CI spectra using the MIKES technique (*V18*).

GC/MS is now employed routinely in investigations of the metabolism of steroid hormones, of which the primary mineralocorticoid, aldosterone, and its immediate stable precursor, 18-hydroxy-11-deoxycorticosterone, have been the subject of recent studies. In an effort to prepare reference samples of ring-A reduced and 21-deoxy metabolites for structural confirmation purposes, Shackleton, Honour, and co-workers have explored the use of anaerobic bacteria for this purpose; *Clostridium paraputrificum* was found to reduce quantitatively various 18-hydroxylated 3-keto-Δ^4 steroids to the corresponding 3α-hydroxy-5β metabolites, while aldosterone underwent 21-dehydroxylation in addition to ring A reduction (*V7*, *V25*). A combination of analytical techniques, including direct insertion mass spectrometry and GC/MS, was employed to identify an unusual C_{21} steroid, 19-nor-11-deoxycorticosterone, in the urine of rats with regenerating adrenals (*V14*). Although this compound is known to be a potent mineralocorticosteroid, its role, if any, in the pathogenesis of human hypertension remains to be established. Steroid metabolism in testis tissue has been studied by Ruokonen, who employed GC/MS to demonstrate the formation in vitro of 5-androstene-3β, 17β-diol, androstenedione, and testosterone from dehydroepiandrosterone, pregnenolone, and their respective sulfate esters (*V23*); this study, together with that of Matsui and Hakozaki who investigated the biliary metabolites of androsterone conjugates in female rats (*V19*), provides further evidence that steroid sulfates can undergo a variety of metabolic transformations without prior removal of the sulfate group. Stable isotope labeling techniques have been employed by Shimizu in a study of androgen formation by the microsomal fraction of boar testes. Analysis of the products of incubation of [17α,21,21,21-$^{2}H_4$]pregnenolone by GC/MS revealed the presence of 5-[17β-^{2}H] adrostene-3β,17α-diol as a metabolite (*V26*), while incubation of [17α-^{2}H] pregnenolone under an atmosphere of $^{18}O_2$ was found to lead to the formation of 5-[17β-^{2}H,17α-^{18}O]androstene-3β,17α-diol (*V27*). The results from these experiments are taken to indicate the operation of a novel pathway by which side-chain cleavage of pregnenolone takes place without initial 17α-hydroxylation, although the mechanism by which deuterium in the 17α position of the substrate appears in the 17β position of the product is obscure. Further studies on the coupling between steroid oxidoreductions in vivo have been reported by Cronholm and Rudqvist, who investigated the transfer of deuterium from [17α-^{2}H] estradiol to C_{19} steroids in female rats (*V9*). GC/MS techniques have also been employed by Watabe et al. to study the metabolism in hepatic microsomes from female rats of 1,3,5(10),16-estratetraen-3-ol, a compound previously identified in the urine of women in late pregnancy (*V30*); the results of the investigation showed that the title estrogen was converted to 16,17-epiestriol and estriol via its 16α,17α and 16β,17β epoxides.

The analysis of steroid hormones and their metabolites by GC/MS techniques has traditionally been associated with the development of new derivatization reagents or procedures, a trend which has continued during the present reporting period. The utility of 20,21-cyclic boronate esters for the characterization of aldosterone has been discussed by Gaskell and Brooks, who report on the EI, methane and isobutane CI and FD mass spectra of the methane- and 1-butaneboronate derivatives (*V13*). A procedure for the derivatization of hydroxy- and α,β-unsaturated ketonic steroids using *tert*-butyldimethylsilylimidiazole in the presence of potassium acetate as catalyst has been reported by Blair and Phillipou (*V6*), while dimethylisopropylsilyl ethers have been evaluated by Miyazaki et al. for use in the GC/MS analysis of a wide variety of hydrorelated steroids (*V20*). Analogous sterically crowded trialkylsilyl derivatives have been studied by Quillam and

Westmore (*V21*). Oxime derivatives of steroids, which have been employed extensively for the analysis of ketosteroids by GC/MS, have been shown to undergo an acid-catalyzed exchange reaction whereby an oxime of one type may be converted into another by treatment with the appropriate substituted hydroxylamine hydrochloride in pyridine (*V4*).

The mechanism by which cholesterol is converted into pregnenolone by the adrenal cortex continues to receive widespread attention. A suspected intermediate in the reaction, isolated from incubations with adrenal mitochondria and previously assigned a 20,22-epoxycholesterol structure (*V17* and references therein) has now been shown by GC/MS to be 5α,6α-epoxycholestan-3β-ol (*V31*). Interestingly, this epoxide has been shown to afford an *S*-glutathione conjugate, 3β,5α-dihydroxycholestan-6β-yl-*S*-glutathione, the formation of which is catalyzed by soluble glutathione transferase of rat liver (*V32*). Ikekawa and co-workers have employed a highly purified preparation of bovine adrenocortical cytochrome P-450 for studies of cholesterol side-chain cleavage and have developed a selected ion monitoring GC/MS assay for the pregnenedione produced (*V11*). Using this system, together with ^{18}O labeling procedures, these workers have shown that the isocaproaldehyde formed by side-chain oxidation of cholesterol undergoes exchange of oxygen with water of the medium in an enzyme-catalyzed process (*V12*). Tracer experiments with $^{18}O_2$ have also been employed by Björkhem and Lewenhaupt in order to study the time course of bile acid biosynthesis in rats provided with a bile fistula (*V5*). The labeling patterns of biliaryl cholesterol, cholic acid, chenodeoxycholic acid, and related 7-oxo bile acids were determined by SIM GC/MS, which revealed a preference for the utilization of newly synthesized cholesterol as substrate for bile acid biosynthesis.

CI/MS with methane or helium as reagent has been used in studies of the mechanism of cholesterol ring-A autoxidation (*V1*) and of the role of singlet oxygen in the oxidation of cholest-4-en-3β-ol (*V29*). Selected ion monitoring GC/EIMS procedures have been reported for the assay of cholest-5-en-3β,7α-diol, cholest-5-en-3β,7β-diol, cholest-5-en-3β,25-diol, and cholest-5-en-3β-ol-7-one in small tissue samples; endogeneous cholesterol, whose concentration is determined by GLC, serves as internal standard in the assay (*V24*). Further applications of GC/MS to studies of sterol metabolism include the identification of 7-hydroxylated derivatives of various 3-oxygenated C_{27}-, C_{28}- and C_{29}-sterols produced by rat liver 18000 g supernatant fraction (*V3*) and the characterization of 4,4-dimethyl-5α-cholesta-8,14,24-trien-3β-ol as a product of 14α demethylation of lanosterol in yeast microsomes (*V2*).

A series of papers by Djerassi et al. has reported on the isolation and identification by 360 MHz ^1H NMR and high resolution EIMS techniques of a variety of interesting new sterols of marine origin (*V10*, *V16*, *V22*, *V28*). CI/MS, together with high resolution FD/MS and EI/MS, has been employed in the structural elucidation of a plant growth-promoting factor isolated from *Brassica napus* pollen; this compound, a C_{28} sterol possessing a novel ring-B lactone structure, has been named brassinolide (*V15*).

Lipids. Applications of mass spectrometry to lipid research have been reviewed recently (*W6*) and deal mainly with the analysis of saturated and unsaturated fatty acids, either present in biological media as the free compounds or in the form of triglycerides or phospholipids. Mass spectrometry has now become the technique of choice for the location of double bonds and cyclopropane rings in fatty acids; thus, while sites of unsaturation are not usually located directly by mass spectral analysis, reaction of unsaturated fatty acids with one of a variety of specific reagents leads to the formation of derivatives which exhibit structurally informative fragmentation patterns (*W7*). Pyrrolidide derivatives are gaining popularity in this respect, and frequently afford EI mass spectra which are dominated by intense $M^{+\cdot}$ species, as illustrated in a paper by Valicenti et al. on the identification of C_{20} fatty acids in bovine lens (*W16*). Ozonolysis, followed by esterification, has been employed in conjunction with pyrrolide formation in a study by GC/MS of the monounsaturated long chain fatty acids of *Mycobacterium tuberculosis* (*W13*). *p*-Bromophenacyl esters, on the other hand, have proven useful for the MS characterization of short-chain fatty acids, such as those found in the defensive secretions of arthropods (*W17*), while methyl esters probably remain the most widely used derivative for the analysis of higher molecular weight members, as exemplified by a study of several cyclic fatty acids found in Finnish tall oil (*W4*). The benefits of glass capillary GC/MS, together with on-line data processing, for the analysis of complex mixtures of fatty esters is well illustrated in this latter paper.

GC/MS techniques have also been used to study fatty acid metabolism. 6-Hydroxydodec-3-*cis*-enoic acid has been identified as a terminal metabolite of ricinoleic acid in *Escherichia coli* (*W8*), while cyclopropanecarboxylic acid has been found to undergo chain elongation in mammals and plants to ω-cyclopropyl fatty acids (*W11*). A method has been published for the quantitative analysis of docosenoic acid in rapeseed oils, based on selected ion monitoring GC/MS with added [1-^{14}C] erucic acid as internal standard (*W1*). Seyama et al. have reported a new GC/MS assay procedure for fatty acid synthetase, in which the amounts of fatty acids synthesized in ^2H_2O are determined, as their methyl esters, by SIM of the characteristic McLafferty rearrangement ions at *m/z* 74 ($[CH_2{=}C(OH){-}OCH_3]^+$) and *m/z* 77($[C^2H_2{=}C(O^2H){-}OCH_3]^+$), using heptadecanoic acid as internal standard (*W12*).

In a comparison of techniques for the qualitative and quantitative analysis of fatty aldehydes by GC/MS, Phillipou and Poulos have investigated the behavior of *O*-methyl and *O*-*tert*-butyldimethylsilyl oximes, in addition to the underivitized species; the authors concluded that the use of CI with underivatized aldehydes is the most satisfactory approach for this class of compounds (*W10*).

tert-Butyldimethylsilyl ethers, however, are being employed increasingly for applications in the lipid field; one recent example has been to the identification by GC/MS of 1,2-*sn*- and 2,3-*sn*-diacylglycerols liberated on phospholipase C treatment of *rac*-phosphatidylcholines (*W9*). Deacylation and acetolysis procedures have been used in a study of the vasopressor phospholipid in crude soyabean lecithin, which was characterized by a number of techniques, including GC/MS, as 1-monoacyl-L-3-glycerophosphate in which the fatty acid residue was mainly linoleic acid (*W14*). Glass capillary GC/MS has been used to identify the major keto acids in arctic bramble following conversion to their 2,4-dinitrophenylhydrazone, methyl ester derivatives (*W5*), while trimethylsilyl ethers were adopted for use in the structural analysis of components of β-diketone-containing plant waxes (*W15*). CIMS has been found to be superior to EIMS for the analysis of carotenoids; in addition to offering enhanced sensitivity of detection, both hydrogen and isobutane CI spectra afford more abundant ions in the high mass region than are observed under EI conditions, while retaining the diagnostic features of the $[M - 92]^+/[M - 106]^+$ ratio (*W2*). The CI mass spectra of underivatized epoxides, hydroperoxides, and epoxy- and hydroxy fatty acids have been recorded using the ion plasma desorption technique developed recently by E. C. Horning and co-workers (*W3*).

The use of [1-^{13}C]palmitic acid as a metabolic tracer for measurement of free fatty acid turnover and oxidation has been evaluated in dogs prior to administration to humans (*W18*).

Vitamins. The advent of high performance liquid chromatography (HPLC) has had a profound impact in the study of vitamin occurrence and metabolism, in that through judicious choice of combinations of straight- and reversed-phase HPLC systems, microgram quantities of the compounds of interest may often be isolated from highly complex biological extracts in a form sufficiently pure for analysis by MS and NMR techniques. This has been true especially for studies in the vitamin A and vitamin D series, where mass spectrometry continues to be an extremely important analytical tool.

4-Hydroxy- and 4-oxoretinoic acid have been identified as in vitro metabolites of all-*trans*-retinoic acid, the carboxylic acid analogue of vitamin A, in hamster trachea and liver (*X4*). Administration to vitamin A-deficient rats of [11,12-^3H] retinoic acid and analysis of the radioactive products which had accumulated in the intestine resulted in the identification of a major component as 5,8-oxyretinoic acid, although the possibility that this compound had been formed as an artifact by acid-catalyzed rearrangement of 5,6-oxyretinoic acid was recognized by the workers involved (*X7*). Subsequently, the same group has demonstrated the presence in rat intestinal

mucosa of the 5,6-epoxide, which is a highly biologically active metabolite of retinoic acid (*X6*), and has shown that formation of this compound in vitro occurs on incubation of all-*trans*-retinoic acid with a variety of rat tissue homogenates (*X10*); in all cases, direct insertion EIMS was employed to verify the structure of the metabolite.

In a study of the biosynthesis of the thiazole moiety of thiamin (vitamin B_1), sugars labeled specifically with ^2H or ^{13}C were fed to *Escherichia coli* growing on defined medium. The position and extent of incorporation of the labels into the 4-methyl-5β-hydroxyethylthiazole portion of thiamin and other cellular components were then determined by GC/MS, which showed that the contiguous five-carbon unit of this portion derived from pyruvate and a triose phosphate (*X12*).

Investigations of the metabolic fate of vitamin D_3 have been stimulated by the mounting evidence which suggests that metabolism of this compound is necessary for the expression of its physiological activity. Two new metabolites, both of which represent products of side-chain oxidation, have been isolated from in vivo studies and purified by extensive chromatographic procedures. Direct insertion low and high resolution EIMS analyses were then used, in conjunction with a number of other physicochemical techniques, to identify the metabolites as 25-hydroxyvitamin D_3 26,23-lactone (isolated from the blood plasma of chicks given vitamin D_3) (*X14*) and 1α-hydroxy-23-carboxytetranorvitamin D (isolated from the intestine and liver of rats given radiolabeled 1α,25-dihydroxyvitamin D_3 (*X3*). A number of studies have concentrated on the properties of hepatic vitamin D_3 25-hydroxylase, all of which have employed mass spectrometric techniques (*X1*, *X2*, *X5*), while DeLuca and co-workers have reported recently that the placenta, in addition to the kidney, is capable of converting 25-hydroxyvitamin D_3 to the active form, 1α,25-dihydroxyvitamin D_3 (*X8*). The use of ^2H NMR and mass spectrometry for the investigation of the vitamin D_3 – previtamin D_3 equilibrium has been described by Zaretskii et al. (*X9*) and procedures for the synthesis of vitamin D_3 metabolites, labeled in the side-chain with three atoms of deuterium, have been published by Whitney and co-workers (*X13*).

Biogenic Amines and Related Compounds. A comprehensive study has been published by Sandler and co-workers (*Y7*) on the metabolism and interrelationships of orally and intraperitonally administered L-dopa, related amino acids and biogenic amines in the rat; GC/MS techniques were employed to identify a wide range of metabolites and to quantify selected examples where electron-capture GLC assays proved inadequate. Hashimoto and Miyazaki (*Y8*) have reported on a stable isotope dilution assay procedure for the simultaneous determination in biological samples of endogeneous norepinephrine and of dopamine β-hydroxylase activity, based on the use of [$^2H_2$] dopamine as substrate, [$^2H_6$]epinephrine as internal standard, and quantification by selected ion monitoring GC/MS in the CI (isobutane or ammonia) mode. A radioimmunoassay for melatonin has been validated by comparison with the GC/negative ion CIMS assay reported by Lewy and Markey (*AF7*), while the related pineal indole derivatives 5-methoxytryptophol (*Y5*) and 5-methoxytryptamine (*Y4*) have been measured by selected ion monitoring GC/MS procedures using a structural analogue and a deuterium-labeled analogue of the compound-of-interest, respectively, as internal standard. Artigas and Gelpi (*Y2*) have reported on the development of similar methodology for the quantification of tryptophan, tryptamine, indole-3-acetic acid, serotonin, and 5-hydroxyindole-3-acetic acid in samples of rat brain. Straightforward procedures for the synthesis of deuterium labeled analogues of a number of biologically-important indolealkylamines have been published by Räisänen and Kärkkäinen (*Y12*). Further studies on this class of compounds involving mass spectrometry have dealt with the identification of 1,2,3,4-tetrahydro-β-carboline as an endogeneous constituent of rat brain (*Y3*) and the quantitative analysis of indole-3-acetic acid in xylem sap of *Ricinus communis* L. (*Y1*).

Histidine and 1,4-methylhistidine have been found to undergo decarboxylation on treatment with pentafluoropropionic acid anhydride, as indicated by GC/MS analysis of the products obtained (*Y11*), although no such effect was observed on derivatization of histamine (*Y11*), 1,4-methylhistamine (*Y11*), or *tele*-methylhistamine (*Y10*), the product of enzymatic methylation of histamine. The gas chromatographic and mass spectrometric properties of trimethylsilyl derivatives of a series of catecholamines have been surveyed (*Y9*). Several biologically-important phenylethylamines have been assayed as their *N*-dinitrophenyl, *O*-trimethylsilyl derivatives by selected ion monitoring GC/MS using methane or isobutane CI conditions (*Y6*).

Cannabinoids. Grote and Spiteller (*Z2*, *Z3*) have described the identification, by glass capillary GC/MS, of a number of new cannabinoids in extracts of cannabis and hashish. These include water-soluble compounds which have been named C_3-cannabichromanone, C_3-cannabielsoin, and C_3-cannabielsoic acid, together with a benzofuran derivative, cannabicoumaronon. The presence of relatively large amounts of cannabinoid acids in these extracts was noted by the authors. Acidic metabolites of cannabinol in rat feces have been identified by Widman and co-workers (*Z11*), who employed packed column GC/MS to characterize six such components, of which the major was cannabinol-7-oic acid.

Microbiological oxidation of cannabinoids has been investigated by two groups. Christie et al. (*Z1*) demonstrated the transformations of Δ^9-THC by *Chaetomium globosum* into a number of products, including the 3′-hydroxy, 11-hydroxy, and 3′,11-dihydroxy derivatives, while Robertson and colleagues (*Z9*) applied GC/EIMS and GC/CIMS techniques to characterize alcoholic and acidic metabolites of cannabidiol produced by *Syncephalastrum racemosum* and *Mycobacterium rhodochrous*.

Palmitic and oleic acid conjugates of 4″-hydroxy-, 5″-hydroxy- and 7-hydroxycannabinol have been identified as metabolites of cannabinol in the rat (*Z10*). *O*-Glucuronide conjugates of 5′-hydroxy-Δ^9-THC and 11-hydroxy-Δ^9-THC have been synthesized using an immobilized UDP-glucuronyltransferase (*Z8*); following conversion to the per-trimethylsilyl or methyl ester/trimethylsilyl ether derivatives, the conjugates were characterized by GC/MS using EI or ammonia CI techniques. An interesting account has been given by Levy et al. (*Z6*) of the identification of a *C*-glucuronide of Δ^6-THC as a metabolite of Δ^6-THC in the mouse. This conjugate, which was resistant to enzymatic hydrolysis by β-glucuronidase, was analyzed by GC/MS as its methyl ester/tetraacetate derivative, when it was found to be identical to the synthetic Δ^6-THC-4′-glucuronide derivative.

The combined application of deuterium labeling and GC/MS techniques to the study of cannabinoid metabolism has been illustrated in a paper by Harvey and Paton (*Z4*), while a stable isotope dilution GC/CIMS assay procedure for Δ^9-THC, 11-hydroxy-Δ^9-THC and 11-nor-Δ^9-THC-9 carboxylic acid in plasma has been described by Hidy and co-workers (*Z5*); the use of glass capillary GC columns was found to be essential in the latter study in order to resolve the Δ^9-THC derivative from an interfering endogenous component. In an investigation of the effects of cannabis extracts and Δ^9-THC administration on the excretion of androgenic steroids and their metabolites in the male rat, Novotny et al. (*Z7*) employed glass capillary GC and GC/MS to analyze blood and urinary steroids; significant changes were observed following treatment of the animals, the cannabis extracts being more active than mixtures containing the same amounts of synthetic cannabinoids.

Prostaglandins and Related Compounds. The use of GC/MS techniques in studies of the products of arachidonic acid metabolism has, in the past, been one of the most rewarding applications of mass spectrometry in the biological sciences. The present reporting period has been no exception in this regard and has witnessed the structural elucidation of an important new class of C_{20} fatty acids, the leukotrienes. In a most elegant study (*AA12*), Murphy, Hammarström, and Samuelsson isolated from murine mastocytoma cells a "slow-reacting substance" SRS, whose existence has been recognized for over 40 years but whose chemical structure has hitherto remained elusive. Following extensive chromatographic purification, a variety of techniques was employed to investigate the structure of SRS, of which microscale chemical degradations followed by GC/MS analysis of the products liberated contributed greatly to the identification of SRS as a cysteine-containing derivative of 5-hydroxy-7,9,11,14-icosatetraenoic acid, conjugated via a thioether linkage at C-6. This work led to the formulation of a new pathway of arachidonate metabolism, leading through 5-hydroperoxy-6,8,11,14-icosatetraenoic acid (5-HPETE) to an unstable

conjugated triene epoxide (leukotriene A) which, in turn, can either undergo hydration to 5,12-dihydroxyicosatetraenoic acid (leukotriene B) or conjugation with cysteine to SRS (leukotriene C). An SRS has been independently identified as the dipeptidyl arachidonic acid structure (not leukotriene C) by study of the first mass spectrum of the intact natural product (*AA11a*). The structure of the lung-derived compound of relevance to asthma (SSR-A) has also been determined by the same method (*AA11b*).

Studies on the formation of prostacyclin (PGI_2) have generally relied on the identification by GC/MS of its stable hydrolysis product, 6-oxoprostaglandin $F_{1\alpha}$; this approach has been adopted by Wharton et al. (*AA26*) to demonstrate pronounced regional differences in prostacyclin formation by rabbit kidney, and by Watanabe et al. (*AA25*) to show that PGI_2 is the primary reaction product obtained from the incubation of PGH_2 with prostacyclin synthetase from rabbit aorta microsomes. The biosynthesis of thromboxane B_2 (TXB_2) in guinea-pig uterine homogenates (*AA17*) and rabbit peritoneal polymorphonuclear leucocytes (*AA4*) has been studied by GC/MS; the former paper is of interest from an analytical standpoint in that the authors used a combination of derivatives, including the methyl ester, trimethylsilyl ether, *O*-butyloxime of TXB_2 for structural verification purposes.

Several studies on the conversion of arachidonate into various prostaglandins have employed GC/MS techniques for both identification and quantification of metabolites. Pace-Askiak and Rangaraj (*AA15*) have investigated PG biosynthesis and catabolism in the lamb ductus arteriosus when the production of PGE_2, $PGF_{2\alpha}$, and 6-oxo-$PGF_{1\alpha}$ was determined by means of stable isotope dilution GC/MS assay procedures. Similar analytical techniques were adopted by Oates and co-workers (*AA8*) who studied the effects of feeding ethyl-dihomo-γ-linolenate on the production of PGE_1 and PGE_2 by rabbit kidney preparations; in this case, PGE_2 was analyzed by GC/MS as its methyl ester, *O*-methyloxime, bis-acetate derivative, while PGE_1 was converted into the methyl ester, trimethylsilyl ether of PGB_1. Prostaglandin, prostacyclin, and thromboxane synthesis by sheep lung microsomal preparations has been demonstrated by Tai et al. (*AA23*) who employed glass capillary GC/MS for metabolite identification.

The mechanism of the prostaglandin synthetase-dependent co-oxidation of diphenylisobenzofuran has been investigated using ^{18}O-labeling techniques, which demonstrated that the reaction is peroxidatic, utilizing PGG_2 as the hydroperoxide substrate, and that the source of the oxygen introduced into diphenylisobenzofuran is from atmospheric oxygen (*AA9*). A novel epoxy-hydroxy carboxylic acid has been isolated from incubations of arachidonic acid with washed blood platelets from human, horse, cat, dog, and rabbit and has been characterized by GC/MS (both before and after reduction with lithium aluminum hydride) as 10-hydroxy-11,12-epoxy-eicosa-5,8,14-trienoic acid (*AA24*). Ogino et al. have isolated from bovine vesicular gland cytosol an activator of prostaglandin hydroperoxidase which was shown on mass spectrometric analysis to be uric acid (*AA14*).

A number of papers, mainly from the Upjohn Company, have described the metabolic fate of PGI_2. Sun and Taylor employed GC/MS techniques to identify seven metabolites of [11-^{3}H]PGI_2 in rat excreta, all of which were related structurally to 6-oxo-$PGF_{1\alpha}$ (*AA20*). It was shown subsequently, however, that oxidation of PGI_2 by 15-hydroxy prostaglandin dehydrogenase is a quantitatively more important reaction in vivo than is the spontaneous hydrolysis of prostacyclin to 6-oxo-$PGF_{1\alpha}$ (*AA21*). In vitro metabolism of PGI_2 has been studied using the isolated rabbit lung (*AA28*) and rabbit kidney (*AA29*), when GC/MS was again employed to identify the products. Pathways of metabolism of TXB_2 in the guinea pig have been reported by Svensson (*AA22*), who also described a selected ion monitoring GC/MS assay procedure for 2,3-dinor-TXB_2, the major urinary metabolite of TXB_2 in this species, based on the use of [$^2H_8$]2,3-dinor-TXB_2 as internal standard.

Studies on the metabolic fate of "classical" prostaglandins continue to rely heavily on GC/MS techniques, as exemplified in a detailed analysis of the urinary metabolites of PGD_2 in the monkey (*AA5*); an important finding in this work was that many of the PGD_2 metabolites possessed the prostaglandin F (cyclopentane-1,3-diol) ring structure, thus indicating that quantitative measurements of PGF-type metabolites in urine may lack specificity for the estimation of PGF biosynthesis in vivo. Powell and Solomon (*AA16*) have characterized a number of 20-hydroxy derivatives as metabolites of E and F series prostaglandins formed in lungs of pregnant rabbits, while a previously unknown metabolic pathway by which PGF_α derivatives may be converted by oxido-reduction into prostaglandins of F_β stereochemistry has been detected in a study of the metabolism of $PGF_{2\alpha}$ in the rat (*AA3*). Incubation of PGG_2 with aortic microsomes was found to yield two products, one of which was identified by GC/MS as 6-oxo-$PGF_{1\alpha}$ and the other as 6,15-dioxo-$PGF_{1\alpha}$ (*AA19*).

A procedure for the quantitative analysis of PGE_1 in biological samples containing a high concentration of PGE_2 and/or 13,14-dihydro-PGE_2 has been described by Goldyne and Hammarström (*AA6*); PGE_1 is isolated by thin-layer argentation chromatography and analyzed by selected ion monitoring GC/MS using [3,3,4,4,5,6-$^2H_6$] PGE_1 as internal standard. An alternative approach to the assay of PGE_1, in which removal of PGE_2 and 13,14-dihydro-PGE_2 is effected by reversed-phase HPLC, has been published by the Vanderbilt group (*AA27*).

New trialkylsilyl ether derivatives have been evaluated for use in the GC/MS analysis of prostaglandins (*AA10*), while the GC and MS characteristics of two existing silyl ether derivatives, the trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (*t*-BDMS) ethers, have been compared for use in the identification of prostaglandin metabolites (*AA2*). The direct derivatization of prostaglandins of the E and A series with a mixture of BSTFA and piperidine has been shown to lead to the formation of 9-enol TMS and 11-piperidyl-9-enol TMS derivatives, respectively (*AA18*). The EI mass spectra of the 11-piperidyl-9-enol TMS PGA derivatives are noteworthy for their simplicity, and exhibit intense $[M - 173]^+$ fragment ions. The utility of CIMS for the characterization of prostaglandins of the A, B, and E series has been discussed by Ariga et al., who advocate the use of ammonia as reagent gas over methane or isobutane (*AA1*). The same workers reported on the application of ammonia CI for the identification of TXB_2 and 6-oxo-$PGF_{1\alpha}$ by GC/MS (*AA11*). However, it should be noted that the EI mass spectrum of the TXB_2 derivative illustrated in this paper is actually that of the 6-oxo-$PGF_{1\alpha}$ derivative, and vice versa. Both high and low resolution EIMS techniques are widely employed in studies on prostaglandin synthesis, of which papers on the synthesis of PGI_3 (*AA13*) and on the tautomerism of the enedione system of 15-oxo-PGD_2 (*AA7*) may be cited as examples.

Miscellaneous Applications. Mass spectrometry has been employed in studies of a great diversity of compounds of biochemical interest, in addition to those classes cited above, ranging from the simple molecule CO_2 to complex polyfunctional natural products. The two-carbon hydrocarbon ethylene, which is known to be a natural plant growth regulator, has been found recently to undergo metabolic conversion in pea seedlings to a product which was identified by GC/MS as ethylene glycol (*AB2*); propylene was similarly metabolized in the same system to 1,2-propanediol. The role of oxidative metabolism in mediating the biological activity of ethylene in plants remains unknown, although evidence is accumulating which would suggest that metabolic "activation" of this olefin is indeed required for expression of growth-stimulating properties. A compound which has been found to arrest the growth of cells in both roots and shoots in the G_2 stage of the cell cycle has been isolated and identified by direct insertion EIMS as *N*-methylnicotinic acid (*AB6*); this appears to be the first example of the identification of a "hormone" which effects cell arrest in complex plant tissues.

2-Decen-1-yl-acetate has been identified by GC/MS as a new alarm pheromone in the stings of *Apis dorsata* and *A. florea* (*AB17*). Biosynthetic pathways in bark beetles to the pheromone ipsenol have been studied by specific deuterium labeling and GC/CIMS methods, which showed not only that the related diterpene ipsdienol was the precursor to ipsenol, but that the biotransformation is enantioselective and is accomplished by male insects only (*AB7*). GC/MS techniques have also been employed to identify two new toxic 12,13-epoxytrichothecenes isolated from the culture filtrates of isolates of *Fusarium roseum* (*AB10*) and to study products of photodecomposition of the pyrethroid permethrin (*AB8*).

In a program aimed at the development of methodology for the analysis of metabolites of the isoquinoline alkaloid apomorphine, Evans and Vouros (*AB5*) have studied the GC/MS

characteristics of *N*-heptafluorobutyryl-*O*-trimethylsilyl derivatives of hydroxynorapomorphines whose EI mass spectra were found to exhibit structurally diagnostic fragmentation patterns. Van Mansvelt and co-workers have reported a method for the identification of ergot-peptide alkaloids, based on GC/MS analysis of the series of peptide degradation products generated on pyrolysis (300 °C) of the parent compound in the injection port of the GC (*AB16*). An identical approach was employed by Plomp et al. who describe the use of this technique for the structural elucidation and quantitative analysis of the thermal degradation products of dihydroergotoxine alkaloids (*AB11*).

^{15}N- and ^{18}O-labeling studies have been used, together with isotope ratio MS, to study the mechanism by which ammonia is converted to nitrite by *Nitrosomonas*; hydroxylamine was identified as the intermediate in this process and it was shown that the oxygen atom which had been introduced was derived from $^{18}O_2$ and not from $H_2{}^{18}O$ (*AB3*). ^{18}O-Labeling has also proved valuable in studies of a variety of enzymatic and chemical reactions, e.g., CO_2 kinetics in red cell suspensions (*AB14*), fructose 1,6-bisphosphatase-catalyzed exchange of oxygen between water and inorganic phosphate (*AB13*), and the stereochemical course of thiophosphoryl group transfer mediated by nucleoside phosphotransferase (*AB12*). An asymmetric synthesis of [1(R)-^{16}O,^{17}O,^{18}O]phospho-(*S*)-propane-1,2-diol has been described and the absolute configuration of the product determined in a procedure involving linked-scan metastable ion MS (*AB1*). Use of this compound as tracer should permit detailed stereochemical and mechanistic studies to be undertaken of the course of many enzymatic and chemical processes involving phosphate.

A procedure for the determination of urinary oxalic acid and of oxalate pool size by stable isotope dilution GC/MS has been evaluated in dogs prior to use in human studies (*AB4*). The use of [^{15}N]glycine as an in vivo kinetic tracer for determination of glycine pool size, turnover rate, and flux has been evaluated in rabbits (*AB9*); the degree of ^{15}N enrichment in plasma glycine samples was determined by GC/EIMS analysis of the *N*-trifluoroacetyl, *n*-butyl ester derivative by rapid repetitive scanning over the mass range *m/z* 125–129 to detect the characteristic fragment ion, $[C_3H_3NOF_3]^+$, formed by cleavage β to the amino nitrogen atom. The results of this study pointed to the suitability of this approach to studies of glycine kinetics in human subjects. A preliminary application of mass spectrometry/mass spectrometry (MS/MS) to the identification of natural products in *Psilocybe cyanescens* has been reported by Unger and Cooks, who demonstrate the utility of the technique in allowing the identification of protonated psilocin in the presence of other compounds with the same mass (*AB15*).

CLINICAL CHEMISTRY

General. The major areas of application of mass spectrometry in clinical chemistry have been summarized in a recent review by Liebich (*AC21*). These are: (1) the identification of unknown constituents, of endogeneous or exogeneous origin, in biological fluids, (2) metabolic profile analysis as a technique for the diagnosis of a variety of pathological conditions, (3) quantitative analysis of specific compounds in body fluids, and (4) qualitative and quantitative analysis of stable-isotope-labeled compounds in metabolic studies. While most of these activities are still confined to specialized laboratories with appropriate instrumentation, mass spectrometric techniques in general, and GC/MS methods in particular, are now gaining widespread acceptance in clinical toxicology and forensic science laboratories for routine drug screening programs (*S14*, *S71*). Indeed, several manufacturers of mass spectrometry equipment have recently introduced low-cost GC/MS/COM systems designed specifically for use in a clinical environment (*AC15*).

The development of definitive and reference methodology, based on mass spectrometric techniques, is an area of growing importance in clinical chemistry, as discussed in some detail in the previous review of this series (*S13*). Definitive methods for the steroid hormones estradiol, estriol, testosterone, progesterone, aldosterone, and cortisol, based on isotope dilution GC/MS assays employing ^{14}C-labeled analogues of the hormones as internal standards, have been reviewed by Siekmann (*AC31*). Two candidate definitive methods for serum cholesterol, one based on the use of GLC with glass capillary columns and the other on selected ion monitoring GC/MS with [3,4-$^{13}C_2$]cholesterol as internal standard, have been compared by Maume, Padieu, and co-workers (*AC12*). A ^{13}C-labeled analogue has also been proposed for use as internal standard in a definitive GC/MS method for glucose in human serum, while an analogous method for serum uric acid employed [1,3-$^{15}N_2$]uric acid for this purpose (*AC4*). Lawson et al. (*AC22*) have reported on a specific method for determining uric acid in serum using high performance liquid chromatography and GC/MS; [1,3,9-$^{15}N_3$]uric acid is employed as internal standard in the assay, which may also be performed by direct insertion MS analysis (*AC20a*).

The application of MS to the qualitative and quantitative analysis of endogeneous compounds in human biological fluids has been the subject of numerous investigations during the present reporting period, many of which are cited in sections *AD–AG*. The concept of "metabolic profiling" has been outlined in an excellent review by Gates and Sweeley (*AC13*), who discuss historical aspects of the technique, tracing its development over the past 40 years to include first GLC, then GC/MS, and finally sophisticated computerized GC/MS methodology. Metabolic profiles of numerous types of compounds found in uremic serum have been presented in a recent publication by Schoots et al., who employed glass capillary columns and both EI and CIMS (*AC30*).

The presence in human plasma of retinoic acid, the carboxylic acid analogue of vitamin A, has been demonstrated by a combination of HPLC and GC/MS techniques; the plasma concentration of this compound was estimated by selected ion monitoring GC/MS to be in the range 1–3 ng mL^{-1} (*AC9*). Vitamin D_3 concentrations in human serum (*AC2*, *AC35*) and plasma (*AC7*) have also been determined by SIM procedures which have indicated that circulating levels are in the order of 5–11 ng mL^{-1}, a range lower than that reported by competitive protein binding assays. The method of Zagalak et al. (*AC35*) measures, in addition, 25-hydroxy-vitamin D_3.

Analysis of monosaccharides and monosaccharide derivatives in human seminal plasma by glass capillary GC/MS has led to the identification of 21 different compounds of which 12 had not been detected previously in semen (*AC33*). Isobutane CIMS has been employed to characterize D-arabinitol as a major metabolite of *Candida* species in human subjects (*AC18*); mass spectra of the underivatized compound and its trimethylsilyl ether were recorded using the direct insertion technique when a deuterium exchange procedure was employed to reveal the number of labile hydrogen atoms (*AC18*). Compernolle et al. have applied mass spectrometry (direct insertion EIMS, GC/EIMS, and FD/MS) to an investigation of glucuronic acid conjugates of bilirubin-IXa in normal and post-obstructive human bile (*AC6*). The conjugate originally secreted is characterized as a 1-*O*-acyl-β-D-glucopyranuronic acid glycoside, which is shown to be converted in post-obstructive bile into 2-, 3-, and 4-*O*-acylglucuronides (*AC5*). GC/MS has been used in a search for hemopyrrole and kryptopyrrole in urine from normal subjects and schizophrenic patients, although the method (limit of detection 100 $\mu g\ L^{-1}$) failed to reveal the presence of either compound in any of the samples (*AC14*). A GC/MS method has been described for the determination of lipid A and endotoxin in serum, based on SIM of β-hydroxymyristic acid, the most commonly occuring β-hydroxy fatty acid in Gram-negative bacteria (*AC23*).

Several recent publications have dealt with the quantitative analysis of amino acids in physiological fluids. Padieu and co-workers (*AC10*) have discussed the use of glass capillary GC columns and isobutyl ester, *N*(*O*)-heptafluorobutyrate derivatives for this purpose, while Kingston and Duffield (*AC19*) report on the development of an assay for 16 α-amino acids in human plasma using selected ion monitoring GC/CIMS and ^{13}C-labeled amino acids as internal standards. The preparation of amino acids labeled in the carboxyl moiety with two atoms of ^{18}O has been described by Murphy and Clay (*AC27*), who discuss the advantages of this approach for the synthesis of stable-isotope-labeled amino acids for use as internal standards in GC/MS assay procedures. Matthews et al. (*AC24*) have assessed the degree to which isotope excess can be determined in ^{15}N-, ^{13}C-, ^{18}O- or ^{2}H-labeled amino acids by selected ion monitoring GC/MS. *N*-Acetyl, *n*-propyl esters were employed in this study, together with methane CI which affords intense MH^+ ions for these derivatives. The results

showed that by using ^{15}N-labeled amino acids, an isotope excess of 0.08 atom % could be determined in plasma amino acids isolated from samples of less than 100 μL in volume. This finding may be compared with that of Robinson et al. (*AC27a*) who report that the isotope content of amino acids labeled with ^{15}N at a level of 0.1 atom % excess may be determined at the 0.1 nmol level by SIM GC/CIMS. In an application of the former methodology, whole-body leucine and protein turnover has been determined in human subjects given an i.v. infusion of L-[1- ^{13}C]leucine (*AC25*). Further examples of the use of stable isotopes as tracers in studies of amino acid metabolism in humans have been described by Hoskins and Pollitt (*AC17*), who have employed deuterated phenylalanine and tyrosine.

The uptake of oleic and elaidic acids into human erythrocytes, platelets, and phospholipids has been studied by Emken and co-workers using deuterium-labeled fatty acids as metabolic tracers (*AC11*). Compounds labeled specifically with stable isotopes have also been employed as tracers in investigations of the metabolism and turnover in humans of bile acids (*AC16*), prostaglandin $F_{2\alpha}$ (*AC3*), catecholamines (*AC1*) and neurotransmitters (*AC20*). The use of $^{13}CO_2$ breath analysis for the assessment of the effect of liver disease on hepatic drug metabolism has been validated in a study in which both healthy subjects and patients suffering from liver disease were administered a mixture of ^{13}C- and ^{14}C-labeled aminopyrine (*AC28*). The labels were excreted at nearly identical rates, as indicated by measurement of $^{14}CO_2$ by radioactivity determinations and of $^{13}CO_2$ by isotope ratio mass spectrometry. A microprocessor-controlled mass spectrometer for the fully automated purification and isotopic analysis of breath CO_2 has been described recently by Schoeller and Klein (*AC29*).

Several reports have appeared on the application of MS techniques to the identification of contaminants in biological specimens, originating from sources such as the cork backing of foil-lined sample vial caps (*AC8*), rubber seals in the aluminum caps of bottles used for storage of blood samples (*AC26*), and rubber disks in the closures of polyethylene bottles containing solutions for intravenous administration (*AC34*).

Steroids, Sterols, and Bile Acids. Two valuable reviews of the use of mass spectrometry for both qualitative and quantitative studies of steroid hormone biosynthesis and metabolism have been published recently by Adlercreutz (*AD1*) and Adlercreuz and Järvenpää (*AD2*). In the former, a detailed discussion is given of current techniques for the isolation, purification, derivatization, and identification of hormonal steroids, with an emphasis on neutral steroids and estrogens; MS approaches to the quantitative analysis of steroids in physiological fluids are also discussed and compared with alternative techniques based on radioimmunoassay. The second review (*AD2*) is oriented more toward the uses of MS in problems in clinical endocrinology, and includes a survey of steroid hormone assays based on selected ion monitoring GC/MS procedures.

In a continuing series of papers on steroid metabolism in the neonatal period, Shackleton and co-workers have reviewed the major differences between the profile of metabolites characteristic of the human fetus and those in the neonatal infant and adult (*AD23*). GC/MS techniques have been employed extensively in these studies, which have included an investigation of qualitative and quantitative differences in the metabolism of corticosterone by the newborn and adult human (*AD11*). Analysis of the urinary metabolites of cortisone acetate in a female infant with 21-hydroxylase deficiency resulted in the identification of eight new ring-A reduced products which were hydroxylated at either C-1 or C-6 (*AD27*). These steroids were also detected in the urine of normal neonates. In an independent study, Derks and Drayer (*AD7*) also demonstrated the presence in human neonatal urine of polar corticosteroid metabolites hydroxylated in the 6-position; comparison of the GC/MS properties of these metabolites with synthetic reference compounds (*AD6*) led to their identification as 6α-hydroxytetrahydrocortisone, 6α-hydroxy-20α-cortolone, and 6α-hydroxy-20β-cortolone.

Spiteller et al. have reported on the use of glass capillary GC/MS for the analysis of steroid metabolite profiles in a number of pathological conditions; these have included studies of urinary steroids in women suffering from idiopathic hirsutism (*AD9*), steroids in hemofiltrates and blood of uremic patients (*AD16*), and steroids in plasma and urine from subjects with psoriasis (*AD17*). Glass capillary GC/MS was also employed by Ulick and co-workers (*AC28*) in a study of the urinary steroids from two patients suffering from a syndrome indicative of primary mineralocorticoid excess. A marked decrease was noted in the excretion of metabolites bearing an 11-oxo group, pointing to an alteration in these patients of the equilibrium position of the 11β-hydroxysteroid oxidoreductase system.

Recent work by Adlercreutz et al. on estrogen metabolism has included GC/MS studies of the estrogen profile in bile of men and nonpregnant women (*AD3*) and a study of the metabolism of various estrogens by intestinal micro-organisms and by human fecal microflora (*AD13*). The Helsinki group has also reported recently on an analytical protocol for the analysis of the complete estrogen profile in urine, based on the use of liquid-gel chromatographic procedures and GC/MS, and employing ascorbic acid to prevent oxidation of labile components (*AD8*). By means of this approach, 4-hydroxyestriol was identified for the first time in pregnancy urine and its excretion rate determined to be between 25.6 and 60.0 μg $24\ h^{-1}$ in four subjects in the last trimester of pregnancy. Further data supporting previously recognized sex differences in certain aspects of human urinary steroid metabolite profiles have been reported by Pfaffenberger and Horning (*AD20*).

Methods for the isolation of steroids from tissues and body fluids by gel filtration procedures have been reviewed by Sjövall and Axelson (*AD25*), who have pioneered the development of this extremely valuable approach for the purification of steroid hormones and their metabolites for GC/MS analysis. The specificity of multicolumn liquid chromatography as a procedure for the isolation of individual neutral urinary steroids for assay by GLC has been evaluated by GC/MS (*AD21*).

A stable isotope dilution GC/MS assay for urinary progesterone has been described, which utilizes the $M^{+\cdot}$ (*mz* 460) of the 3-enol pentafluropropionyl derivative for quantification by SIM (*AD14*); [7,7-$^2H_2$]progesterone (*AD5*) serves as internal standard in the assay. A further quantitative GC/MS method employing a specifically deuterium-labeled analogue as internal standard has been developed for the measurement of urinary tetrahydrodeoxycorticosterone (*AD22*). In this case, the internal standard was prepared by a simple exchange reaction through which deuterium was incorporated at C-17α and C-21; stability studies demonstrated that no detectable back-exchange of label took place during the procedure used for urinary steroid analysis. Serum estradiol has also been determined by SIM GC/MS, using [2,4,16,16-$^2H_4$]estradiol as internal standard (*AD29*), while an analogous procedure for the quantitative determination of the oral contraceptive 17α-ethinylestradiol relied on the use of a tritium-labeled analogue of the drug as internal standard (*AD24*).

GC/MS techniques have played an important role in the study of bile acid metabolism in humans and have been employed to investigate certain disease states associated with specific defects in the pathways of bile acid biosynthesis or metabolism (*AD26*). Urinary bile acids from three patients with Zellweger's syndrome, a condition associated with severe mitochondrial abnormalities, have been analyzed by Hanson et al. (*AD10*), who demonstrated an excessive excretion of three C_{26} precursors of chenodeoxycholic and cholic acids in these patients. The results of this study, which employed both GC/EIMS and GC/CIMS analysis, confirmed the importance of mitochondrial enzymes in mediating the oxidative cleavage of the cholesterol side-chain. Chemical ionization GC/MS, employing methane as both carrier and reagent gas, has been used in an investigation of the products of metabolism of lithocholic acid-3α-sulfate by human intestinal microflora (*AD15*). The use of dimethylethylsilyl ether, ethyl ester derivatives has been advocated for the analysis of bile acids by SIM GC/MS using open tubular glass capillary GC columns (*AD18*). The relationship between bile acid concentrations in serum (determined by SIM GC/MS) and bile acid pool size has been discussed by Einarsson and co-workers, who compared normal subjects with patients suffering from hyperlipoproteinemia (*AD4*).

Ikekawa et al. (*AD12*) have reported on the identification of a new C_{26} sterol, 22-*trans*-27-norcholesta-5,22-dien-3β-ol, in the serum and urine of a 6-year-old girl with congenital

adrenal hyperplasia of the salt-losing type. This appears to be the first report of the detection of such a compound in mammalian biological fluids, although the origin of the sterol was not established in this study.

Finally, the CI mass spectra of a group of polar steroid hormones have been determined directly using the plasma desorption ionization technique described by E. C. Horning and co-workers (*AD19*). No derivatization is necessary in this approach which should prove useful, when employed in conjunction with appropriate isolation and purification procedures, for the analysis of steroid hormones and their metabolites in biological media.

Prostaglandins and Related Compounds. The balance between the production of prostacyclin (PGI_2), a potent vasodilator and inhibitor of platelet aggregation, and thromboxane A_2 (TXA_2), a potent vasoconstrictor and pro-aggregatory substance, has attracted much attention recently in studies of cardiovascular disease. Both compounds are chemically unstable, however, and undergo hydrolysis in vivo to 6-oxo-$PGF_{1\alpha}$ and TXB_2, respectively. In an investigation of the role of the human lung in the production of prostacyclin, Hensby, Dollery, and co-workers have employed a stable isotope dilution GC/MS assay procedure (*AE1*) to measure concentrations of 6-oxo-$PGF_{1\alpha}$ in blood samples taken simultaneously from the pulmonary artery and left ventricle of five subjects (*AE6*). The results in all cases showed that the concentration of 6-oxo-$PGF_{1\alpha}$ was significantly higher in the left ventricle (207 ± 33 pg mL^{-1}; mean ± SEM) than in the pulmonary artery (131 ± 13 pg mL^{-1}), thus providing strong evidence that the lung releases PGI_2 into the blood flowing through it. An additional study by the same group (*AE4*) demonstrated that plasma concentrations of 6-oxo-$PGF_{1\alpha}$ in 16 male diabetic patients were significantly lower (mean 98.8 pg mL^{-1}) than in healthy control subjects (mean 132.9 pg mL^{-1}), pointing to a deficiency in PGI_2 production in diabetes.

The Upjohn group has reported that a fibroblast of human lung origin synthesizes TXA_2 from the prostaglandin endoperoxide PGH_2 (*AE7*); the TXA_2 released during incubations was identified as its hydrolysis product, TXB_2, by GC/MS of the methyl ester trimethylsilyl ether derivative.

Stimulation of arachidonic acid metabolism in human skin by irradiation with short wavelength ultraviolet radiation (100–290 nm) has been demonstrated by Greaves et al., who employed stable isotope dilution GC/MS assay procedures to measure the concentrations in exudate from normal and inflamed skin of arachidonic acid, PGE_2 and $PGF_{2\alpha}$ (*AE3*). Levels of all three compounds were elevated in the inflamed skin, although prior administration to subjects of indomethacin, either topically or orally, totally suppressed the UV-induced elevation of PGE_2 and $PGF_{2\alpha}$ concentrations (*AE2*).

Glass capillary GC/MS techniques have been developed by Halket et al. for the analysis of prostaglandin profiles in human seminal fluid (*AE5*). Repetitive scanning over the full mass range is employed and individual prostaglandins are detected by use of computer-reconstructed ion current profiles (mass chromatograms). An assay procedure for PGE_2, $PGF_{2\alpha}$, and 7α-hydroxy-5,11-dioxotetranorprostane-1,16-dioic acid in human urine, based on SIM capillary GC/MS, has been published by Seyberth and colleagues (*AE4a*). The authors state that "Compared to packed columns, resolution, sensitivity and specificity were greatly improved by the capillary column."

A review on the role of prostaglandins in the pathogenesis of human disease, with particular emphasis on the use of stable isotope labeling and GC/MS techniques in this field, has been published by Oates (*AE8*).

Biogenic Amines and Related Compounds. The great majority of applications of mass spectrometry in this subject area involve quantitative determinations by SIM GC/MS of specific biogenic amines and/or their metabolites in physiological fluids. An impressive illustration of the high sensitivity attainable by negative ion CI techniques is given in a paper by Lewy and Markey (*AF7*) describing the measurement in small samples of human plasma of the pineal indolealkylamine, melatonin, at concentrations as low as 1 pg mL^{-1}. [$^2H_4$]Melatonin serves as internal standard in the assay, which employs, for SIM purposes, the stable spirocyclic derivative produced on treating melatonin with pentafluoropropionic acid anhydride. Methane is used as both GC carrier gas and CI reagent gas in the assay, which is reported to be approximately 150 times as sensitive as an equivalent positive ion GC/CIMS method based on the use of the same derivative and reagent gas. Brief details of an alternative SIM assay for melatonin and 5-methoxytryptophol in human plasma, in which electron impact ionization is used, have been reported in abstract form (*AF6*); however, no information is given on the sensitivity of this method, although it has been employed for the determination of plasma melatonin in children in the early stages of puberty where concentrations are up to 1000 times greater than the normal adult range. Further applications of GC/MS to the analysis of endogeneous indole derivatives have been to the quantification in human serum of tryptophan, *N*-acetyltryptophan, and kynurenine (*AF18*) and to the verification of a GLC assay for *N*,*N*-dimethyltryptamine (DMT) and *N*-monomethyltryptamine (NMT) in human urine (*AF15*); in the latter paper, SIM was carried out at a mass spectrometric resolution of 6000 (10% valley) to confirm the elemental composition of the MH^+ ion of the trifluoroacetyl derivative of DMT formed under methane CI conditions.

GC/MS assay procedures for catecholamines in human plasma have been reported by Ehrhardt and Schwartz (*AF1*) and Jacob et al. (*AF4*); in the latter method, the use of SIM at high resolution was found to be essential to ensure adequate specificity of detection. An SIM GC/MS procedure has been reported for epinephrine, norepinephrine, and dopamine in human autopsy brain samples, based on the use of α-methyldopamine as internal standard and CI using isobutane as reagent gas (*AF8*). Deuterium-labeled internal standards have been employed in GC/EIMS assays for 5-hydroxytryptophol in human cerebrospinal fluid (*AF16*) and 5-methoxyindole-3-acetic acid in human urine (*AF3*). Numerous papers have appeared on the application of GC/MS techniques to the quantitative analysis of acidic, basic, and neutral metabolites of catecholamines in human body fluids (*AF2*, *AF5*, *AF14*, *AF17*). Muskiet and co-workers have been particularly active in this field and have reported on the development of stable isotope dilution GC/MS assays for various catechol and 4-*O*-methyl catechol metabolites in urine (*AF9–AF11*) and amniotic fluid (*AF12*). Synthetic procedures for the preparation of deuterium-labeled catecholamines, catecholamine metabolites, and tryptophan metabolites for use as internal standards in the above assays have also been reported (*AF13*).

Organic Acids. Several excellent publications have appeared dealing with the application of GC/MS to the study of urinary organic acid profiles in health and disease states. Gates, Sweeley, and co-workers have presented quantitative and qualitative data on the excretion of 134 organic acids in the urine of 9 adult control subjects, 5 juvenile control subjects, and 5 children with neuroblastoma (*AG6a*, *AG7*). In this study, which was performed using the Michigan State University mass spectral metabolite analysis program (MSSMET), 60 endogenous organic acids are positively identified and GC/MS data are presented for an additional 81 substances which were sought but not found by this method. The Oslo research group of Jellum, Stokke, et al. have reported on the chromatographic profile of high boiling point organic acids in human urine from both healthy subjects and patients suspected of having some form of metabolic disorder; GC/MS using Dexsil-300 as stationary GC phase was employed in this investigation which resulted in the identification of two acids, cinnamoylglycine and acetyltributylcitrate, which have not been recognized previously (*AG2*). Smith and co-workers at Stanford University have employed the HISLIB computer program in a comparison of ion-exchange and solvent extraction procedures for use in the analysis of urinary organic acid profiles by computerized GC/MS techniques (*AG6*). A specialized high resolution GC/high resolution MS/computer system has been applied to the analysis of organic acids in human urine in order to evaluate the utility of this extremely powerful technique for complex mixture analysis (*AG14*); the utility of accurate mass data in this type of study is illustrated by the identification of quinic acid in the urine of healthy subjects, and the benefits of glass capillary GC columns for metabolic profiling studies are discussed.

A method for rapid screening of urinary organic acids, based on direct insertion isobutane CIMS of the acidic fraction from urine, has been reported by Issachar and Ynon (*AG10*). The use of a solid-phase extraction procedure for the isolation of organic acids from urine has been evaluated by Anderson et

al. (*AG1*), while adsorption onto silica gel has been studied as an alternative approach to the extraction of organic acids for GC/MS analysis (*AG18*). Hähnel and co-workers have studied organic acids in human amniotic fluid by GC/MS and report on the "normal" metabolic profile in this medium (*AG15*).

O-Trimethylsilylquinoxalinol derivatives are gaining popularity for use in the GC/MS analysis of α-oxo-acids (*AG11*) and have been employed in quantitative determinations of branched-chain α-oxo acids from various physiological sources (*AG4*) and β-phenylpyruvic acid in human cerebrospinal fluid (*AG12*). Adipic, suberic and sebacic acids in human serum and urine have been quantified by selected ion monitoring GC/MS of their trimethylsilyl derivatives using 3,3-diethylglutaric acid as internal standard (*AG8*). Studies on the quantitative analysis of hawkinsin, an unusual sulfur-containing metabolite of tyrosine formed in patients with a defect of 4-hydroxyphenylpyruvate dioxygenase, have revealed unexpected behavior of unlabeled and deuterated forms of the compound on GLC; a partially reversible adsorption of the trimethylsilyl derivatives of the two isotopic species of hawkinsin precluded their use in a conventional stable isotope dilution GC/MS assay, although SIM of 1,4-dihydroxycyclohexylacetic acid, formed by desulfuration of the sample with active nickel, was employed successfully for quantitative measurements (*AG16*).

GC/MS and direct insertion EIMS have been employed to characterize two previously unreported fatty acids isolated from patients with Refsum's disease as unsaturated analogues of phytanic acid, although the locations of the double bonds in these metabolites could not be determined (*AG5*). 5-Hydroxyhexanoic acid has been identified for the first time in human urine when urinary organic acids from twin siblings with a Reye's-like syndrome were analyzed by GC/high and low resolution MS (*AG3*). Further examples of unusual organic acids which have been identified by GC/MS in the urine of children with metabolic disorders include 3′,4′-deoxynorlaudanosolinecarboxylic acid (*AG13*) and 2-deoxyerythropentonic acid, 2-deoxythreopentono-1,5-lactone, and 2-deoxyerythropentono-1,4-lactone (*AG17*). Finally, *cis*-3,4-methylene hexanedioic acid has been detected in the urine from healthy adult subjects and characterized by comparison of its GC/MS properties with those of an authentic sample of the compound; the mean daily excretion of this acid in nine subjects was found to be 88 μmol 24 h^{-1} (*AG9*).

HUMAN AND OTHER BIOLOGICAL TOXIC ENVIRONMENTAL EXPOSURE

While at the present time it is essentially impossible to formulate the nature and extent of the exposure of biology to potentially and factually hazardous substances in our present biosphere, the methods and techniques of microchemistry and mass spectrometry are gradually bringing into focus the nature of the chemical problems of our human ecosystem. It is not the purpose of this review to provide an exhaustive interdisciplinary account of the diverse fields of endeavor which bear on environmental health, both as a human burden and as a human detoxification/excretion problem. However, some of the components of these considerations have been extensively reviewed in their own right recently and will be presented for the readers' consideration.

In a timely endorsement of our vested interests in attempting to understand the nutritional requirements of our civilization, Horman (*AH6*) has pointed out that, despite our "preoccupation with food as a source of energy and pleasure", recent information on the molecular nature of food and its contaminants has been "curiously treated". Since it must appeal to our senses, the aspects of flavor, aroma, color, and texture are important; Horman points out that mass spectrometry is in widespread use for the identification of individual compounds contributing to or responsible for these characteristics. He has further concerns on agricultural procedures (e.g., use of herbicides and pesticides) and technological aspects (e.g., changes in food composition occurring during processing, use of additives, problems of bulk storage and packaging, etc.). He states "it is seen that food chemistry cuts across several subjects from pure natural product chemistry, through plant morphology, and environmental science, to food legislation and consumer protection, and in all these fields examples of mass spectrometry are to be found". Horman's review treats agricultural residues, technological residues, food additives, and environmental residues, as well as secondary metabolites from fungal spoilage of crops. He notes the necessity for more widespread application of data systems in research into this interdisciplinary area.

One aspect of Horman's concern has been treated by Kolor; this is a chapter on the flavor components containing the assertion that the olfactory system can distinguish among thousands of chemicals alone or in combinations, illustrated by the threshold value of 2 parts/10^{12} for 2-methoxy-3-isobutylpyrazine. (The best of new generation mass spectrometers should be just able to compete!) The chapter contains an informative table on the number of different types of organic substances found in fruits, vegetables, dairy products and eggs, meat, fish, poultry, nuts, bread, and other food products such as barley, coffee, popcorn, potato chips, and tea (*AH13*).

A complementary review of about 120 papers appearing in the food literature where mass spectrometry has been employed to measure toxic contaminant levels has recently been published (*AH17*). This deals with nitrosamines, pesticide residues, PCBs, polychlorodibenzodioxins, polycyclic aromatics, polybromobiphenyls, trace chemicals which leak out of packaging material into food during storage, chlorophenols, and mycotoxins. Self points out in his discussion the normal scientific reporting dilemma vis-à-vis proper experimental documentation due to the complexity of the environmental and tissue samples and the required specificity and identity in the assays. He echoes the need for instrumentation of high sensitivity which can be operated at high mass resolution, if necessary, even in the multiple ion detection or entire spectrum mode, since there is a *grave difference* between *detectability* of masses or particular isobars and the *unambiguous identity of the molecular nature of the substance in question*. All of these considerations are important problems in the subnanogram range.

Another review discusses the uses of mass spectrometry in the control of food and consumer articles (*AH7*) and continues with the mass spectral analysis of the most important contaminants and hazardous pollutants in food, as well as the investigation of some consumer articles (*AH8*; 266 references).

Andersson, Lundgren, and Stenhagen (*AH2*) have contributed a recent chapter on pheromones and allelochemics and are quick to point out that the term "pheromone" has a broad context in that intraspecific chemical communication occurs in all the five kingdoms into which the world of organisms has been classified: procaryotes, protists, fungi, plants, and animals. The terminology for chemical signals includes activators such as attractants, arrestants, incitants, stimulants, repressors, repellants, suppressants, deterrants, toxins, and venoms.

The need for analytical methods to identify nitrosamines and to measure their concentration in a variety of substances arises from the fact that most *N*-nitrosamines have been shown to exhibit carcinogenic activity toward many animal species and they are readily formed by the interaction of the appropriate secondary amine and the nitrite ion (*AH5*). Gough (*AH5*) has reviewed, in 200 references, the logical considerations for nitrosamine analyses which can be as stringent as exist for any substance (e.g., TCDD) in the application of the techniques of mass spectrometry, both from a specificity and a sensitivity point of view. The use of glass capillary gas chromatography with selected ion monitoring at M/M 10000 is necessary for even dimethylnitrosamine, for example. The substances monitored are bacon, cured meat products, fish, cheese, tobacco products, air, water, industrial and agricultural chemicals, drugs, and biological fluids. A recent study on the separation of hydroxylated *N*-nitrosamines has been carried out, since it has recently been recognized that various less or nonvolatile hydroxylated nitrosamines are widely distributed or formed in the human environment (*AH14*). Volatile nitrosamines have been characterized in normal human feces (*AH19*).

Sphon and Brumley (*AH18*) have discussed the utility of mass spectrometry for the identification of pesticides and pesticide residues. They have correctly sounded a warning concerning the protocol of experiments in this area . . . "unfortunately the use of the mass spectrometer . . . led to the practice of monitoring of one or more ions characteristic

of the *anticipated* compound, the *assumption* being that a response by the mass spectrometry would provide an *unambiguous identification . . .*" [all italics are reviewer's]. The dangers inherent in this relaxed approach were illustrated using Arochlors and five pesticides.

A review of the application of mass spectrometry to the detection of xenobiotic chemicals in the environment has been prepared by Dougherty (*AH4*), covering both mass spectrometry techniques as well as toxic residues identified in humans and the food chain. A recent discussion of the potential uses of GC/MS in industrial hygiene is very much out of contact with the recent literature and present capabilities of mass spectrometry (*AH3*). A particularly comprehensive chapter on air pollutants has been prepared by Schuetzele (*AH16*), covering both the methodology and substances identified. Two reviews entitled "Environmental Applications of Mass Spectrometry" have appeared. One concerns the 1976 publications reporting organic and spark source mass spectrometric studies (*AH1*; 349 references); the other focuses on the applications and the detection, confirmation, environmental, and metabolic degradation of the major classes of pollutants (*AH15*).

Information on the growing use of stable isotopes of hydrogen, carbon, oxygen, nitrogen, and sulfur as tracers in biological systems and as labels for internal standards for quantitative mass spectrometry has been compiled for the periods 1971–1976 by the Kleins. These bibliographies deal with biological, biochemical, pharmacological, clinical, and environmental uses of deuterium (*AH9*), carbon-13 (*AH12*), nitrogen-15 (*AH10*), oxygen-17, -18 and sulfur-34 (*AH11*). Author and subject indexes are included in this bibliography.

ORGANIC GEOCHEMISTRY

Organic geochemistry involves an interdisciplinary approach, encompassing chemistry, biology, and geology, to studies of the short- and long-term fate of carbon compounds in contemporary environments and the sedimentary geological record. The source of organic matter is that which "leaks out" of the biosphere into the geosphere, principally through its co-accumulation with inorganic material during formation of the sedimentary column. Thus, in oversimplified terms, the suite of "natural products" is transformed by aerobic and anaerobic biological systems prior to compaction in an anoxic sediment of definable mineral composition. A wide variety of molecular transformations occur during (microbiological) and after (mineral catalyzed) sedimentation and are classified grossly as types of processes occurring in the temperature regimes to which the sediment is subjected—diagenesis being up to 50 °C, catagenesis to 200 °C, and metamorphism at higher temperatures. In general, the sedimentary column consists of two types of organic matter: that which is solvent extractable and that which is not. The former is called bitumen and the latter is called kerogen. During catagenesis and metamorphism of kerogen, petroleum is produced. The complexity of the nature of these considerations when viewed from a molecular structure and qualitative compositional point of view would, of course, be overwhelmingly intractable were it not for the power of present and developing techniques of chromatography and all aspects of mass spectrometry.

During this period, two texts have appeared concerning the petroleum aspects of organic geochemistry, one by Hunt (*AI2*) and the second by Tissot and Welte (*AI5*). Eglinton and co-workers have presented an up-to-date overview of the nature of lipids of aquatic sediments, both recent and ancient, with a particular emphasis on the ways in which mass spectrometry has been involved in characterization of these organic geochemicals. This is an excellent introduction to the field (*AI1*). In addition, Simoneit has prepared a chapter on the organic chemistry of marine sediments (*AI4*).

For those interested in a detailed chronicle of achievements, the reader is referred to other reviews in this series. In a recent review, Pillinger (*AI3*; 166 references) has discussed methodology, recent sediments, ancient sediments, kerogen, oil and petroleum, extraterrestrial samples such as lunar soils and carbonaceous meteorites, and stable isotope analysis. The 8th and the 9th International Congresses on Organic Geochemistry have been held in Moscow in 1977 and Newcastle-upon-Tyne in 1979.

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