Advances in Carbohydrate Chemistry and Biochemistry

Editors
MELVILLE L. WOLFROM
and
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Assistant Editor
DEREK HORTON

Volume 24

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PREFACE

In the untimely death of Professor Melville L. Wolfrom on June 20, 1969, the world of carbohydrate chemistry lost a great and inspiring scientist, teacher, and writer. He was an Editor of *Advances in Carbohydrate Chemistry* from its inception in 1945 until his demise, except for 1950–1951 when he served on the Board of Advisors. On the death of Claude S. Hudson in 1952, he became the Editor, with the writer acting successively as Assistant Editor (1953–1954), Associate Editor (1955–1966), and Editor (1967 on). Upon assuming this responsibility, Professor Wolfrom made a firm resolve to continue to adhere to the high standards of scholarship and writing that had been insisted upon by Professor Hudson. The merits of this policy are attested to by the succession of laudatory reviews that every volume of this serial publication has earned. Because of this demonstrated success, it is the intention of the Editor that this policy shall be continued, even though, as Professor Wolfrom dryly remarked in the Preface to Volume 8, "the enforcement of such a policy is not without attendant difficulties."

In every volume of this serial publication, the nomenclature of carbohydrates has presented problems. In their solution, the leadership that from 1951 Professor Wolfrom so ably provided as Chairman of the Carbohydrate Nomenclature Committee (of the Division of Carbohydrate Chemistry of the American Chemical Society) was also of inestimable value in ensuring the use of correct nomenclature in all succeeding volumes of *Advances in Carbohydrate Chemistry*.

In September of 1968, Professor Wolfrom appointed Professor Derek Horton to the position of Assistant Editor, with the understanding that his association with this publication was to commence with Volume 24 (1969). This appointment was made with the intent of preserving continuity as regards the goals and standards already mentioned. At about the same time, he decided to amend the title of the publication in order to make clear that topics in biochemistry are, as indeed they always have been, subjects of discussion herein. Finally, because of the resignation of Dr. R. C. Hockett from the Board of Advisors and the death of Professor S. Peat (a member of the Board of Advisors for the British Isles), he decided to appoint, as replacements, the scientists whose names now appear on the title page and to widen the scope of the latter Board by renaming it the Board of Advisors for the British Commonwealth.

Kensington, Maryland R. STUART TIPSON
September, 1969

In this volume, each of two long and authoritative articles started in Volume 23 is concluded: these contributions are by Isbell and Pigman (Washington and New York) on the mutarotation of sugars in solution and by Ball and Parrish (Natick) on sulfonic esters of carbohydrates. In a masterly account of the nitro sugars, Baer (Ottawa) extends and updates Sowden's related chapter that appeared in Volume 6. Although only four years have elapsed since Ferrier (London) discussed the unsaturated sugars (Volume 20), progress in this field has been so great that he devotes an entire chapter to advances made in the interim. Rees (Edinburgh), in a stimulating discussion of the formation of polysaccharide gels and networks, develops recent ideas on conformations of macromolecules that may well serve to direct the trend of future work in this area. Aspinall (Peterborough) provides a detailed insight into the structure of gums and mucilages concerning important correlations that have been made since the subject was examined in Volume 13. Finally, two topics not hitherto covered are reviewed. Kiss (Basle) contributes a comprehensive summary of the present status of knowledge of the glycosphingolipids, carbohydrate compounds of considerable complexity and biological importance. McGale (Stoke-on-Trent) gives us a necessarily brief description of a little-explored group of substances, namely, the protein-carbohydrate compounds in human urine. An obituary of Richard Kuhn is provided by Baer (Ottawa), a former student of Kuhn's.

The Subject Index was compiled by Dr. L. T. Capell.

Kensington, Maryland R. STUART TIPSON
Columbus, Ohio DEREK HORTON
November, 1969

Structure, Conformation, and Mechanism in the Formation of

Polysaccharide Gels and Networks

D. A. REES

Gums and Mucilages

G. O. ASPINALL

Glycosphingolipids

(Sugar-Sphingosine Conjugates)

J. KISS

Protein-Carbohydrate Compounds in Human Urine

E. H. F. McGale

RICHARD KUHN

1900–1967

Richard Kuhn was born in Vienna, Austria, on December 3rd, 1900. He was the younger of his parents' children, the first being a daughter, Angelika. Richard Clemens Kuhn, his father, was a hydraulics engineer and senior civil servant with the Austrian Government; he planned and executed such projects as canals and harbor facilities, including the modernization of the Adriatic seaport of Trieste, which at the time lay in the realm of the Austro-Hungarian Empire. Richard Kuhn's mother, Angelika (née Rodler), a professional schoolteacher, obtained permission to tutor her son privately at home in lieu of grade school; only once every year was Richard obliged to report for official tests which would ascertain his good progress, and by such expedient and effectual instruction the boy was able to enter high school—the Döblinger Gymnasium—before he had even reached the age of nine. Here he was to develop a life-long friendship with a congenial classmate, Wolfgang Pauli, of later fame in theoretical physics. Gifted teachers, a serene domestic atmosphere in which learning was valued and standards were set by educated parents, and close contact with family acquaintances from among the Viennese university faculty, provided the setting where, in the midst of the cultural metropolis, Kuhn grew through boyhood in carefree, prewar years. He was early initiated to the marvels of chemistry by a friend of the family and noted scholar, Professor Ernst Ludwig, who occupied the chair of medicinal chemistry. Having grown fond of the young adept, Ludwig invited him frequently to watch and assist with the preparations for lecture experiments. Ludwig's textbook of chemistry for aspirants of pharmacy, a present from the author, was the teenager's first, avidly perused, source of the science over which he was to gain such unexcelled mastery in years to come. However, difficult times lay ahead and had to be negotiated with that assiduous dedication which marked Kuhn's entire life before the seeds sown in those formative days could bring forth the wealth of bloom that has so enriched the garden of the natural sciences.

World War I and ensuing defeat, revolution, collapse of traditional values and institutions, and economic turmoil with scarcity of means, galloping inflation, and political disorders of all kinds, held sway during Kuhn's final high-school years and on through university. The seventeen-year old found himself conscripted into the army signals corps. Of robust if portly stature, Kuhn was by no means averse to the outdoors; he played tennis well, loved mountain climbing and, in later years, derived great enjoyment from joining his assistants in ball games upon the Institute lawn. Nevertheless, for those who have known his dignified comportment and civil manners, devoid of any martial and heroic traits, it is a rather incongruous thought to visualize him donning military garb and moving about in a crude barracks milieu that must have been utterly alien to his nature. Good fortune spared him major front-line action, and upon his discharge in November, 1918, he wasted no time in hurrying back to the sources of learning. He speedily managed to be enrolled at the University of Vienna and to be assigned laboratory space which was hard to obtain under the crowded and uncertain conditions of the times. For two semesters, he studied in his home town under W. Schlenk, R. Wegscheider, and A. Franke, whose lectures and courses much impressed him and evoked a lasting high regard for these teachers.

However, from across the border beckoned the climaxing fame of Richard Willstätter, Nobel laureate, who had succeeded to the Munich chair of Adolf von Baeyer and was carrying on the great chemical tradition that had sprung up in the Bavarian capital under Justus von Liebig half a century before. Richard Kuhn moved to Munich, completed with dispatch all undergraduate requirements in three more semesters, and, in 1921, was accepted for doctoral work with Willstätter, whose favorite pupil and assistant he soon became. In November, 1922, a fortnight before his twenty-second birthday, he was awarded the degree of Doctor of Philosophy, *summa cum laude*, having submitted a dissertation "On the specificity of enzymes in carbohydrate metabolism." Willstätter had at the time turned from his classical investigations on the structure and synthesis of natural products toward enzyme chemistry, and Kuhn is credited with having contributed vastly to the master's pioneering studies in this newly developing field. It was Kuhn who introduced into Willstätter's laboratory the concepts and techniques of physical chemistry pertaining to accurate kinetic measurements of enzyme activities, and these were essential for guidance in the processes of isolation and purification. Willstätter quickly realized that here was a man of rare talents, and he invited him to stay on in preparation for an academic career, lending his invaluable support in many ways. The brilliant young scientist was enabled to assert leadership by being allowed to direct students of his own at an unusually early stage. Displaying an enormous propensity for recognizing problems and for solving them with originality and extraordinary experimental skill, he shortly amassed a great many results by independent efforts (although within the general strategy promulgated by Willstätter), and he thus met the rigorous demands attached to his "habilitation"[1] which took place in March, 1925. The thesis was entitled "The mechanism of action of amylases; a contribution to the problem of the configuration of starch."

Less than two years later, Richard Kuhn was called to the Eidgenössische Technische Hochschule in Zürich as full professor of general and analytical chemistry, a post which he occupied for three years (1926-1929). Among the students of pharmacy who took his courses there was one who was, it seems, impressed by more than his prowess at lecturing alone; she was Daisy Hartmann, who married her professor in 1928. The happy union was blessed with six children – two boys and four girls. Of them, Richard Kuhn often spoke with great affection and pride, although otherwise, in his rather introverted manner, he was not given to baring personal feelings too readily. Towards the end of 1929, Kuhn accepted an invitation to become Head of the Department of Chemistry in the newly founded and extremely well-appointed Kaiser Wilhelm Institut für Medizinische Forschung[2] at Heidelberg, where he remained for the rest of his life. He was named Director of the Institute upon the death of its founder, Ludolf von Krehl (1937). He was associated with the University of Heidelberg, first as Honorary Professor in the Faculty of Science, and, from 1950, as Professor of Biochemistry in the Faculty of Medicine.

To gain some appreciation of Richard Kuhn's scope, one may well go back in mind to the day of his habilitation at Munich, in 1925, which appears to have been a highlight in the annals of that great university, forecasting with some poignancy the diversity of potential that became his hallmark. The presentation of a formal lecture on "The position of theory in organic chemistry" was followed by an oral defense, before the faculty, of twelve propositions that covered an amazing range of topics. Among them, of special interest to carbohydrate chemists, were a challenge of the Tollens sugar formula, for

(1) The procedure by which, in German universities, a scholar is accorded the privileges and duties associated with a lectureship.

(2) The Institute originally consisted of departments of chemistry, physiology, physics, and pathology. It was renamed Max Planck Institut in 1950. Otto Meyerhof the biochemist, and Walter Bothe the nuclear physicist, both Nobel prize winners, headed departments for many years.

which Kuhn maintained that proof was lacking, and a criticism of Baeyer's strain theory—sacrosanct in the Munich of the early twenties—which he denounced as having decisively impeded progress in the field of higher alicycles. Other features of the debate included the crystal structure of phosphorus molybdic acids, the magnetic state of chlorine dioxide, aspects of reaction kinetics, displacement mechanisms, heterogeneous catalysis, enzyme-coenzyme dissociation, the action of insulin, and the significance of lactic acid in muscle physiology!

Kuhn's lifetime work, documented in more than seven hundred publications, is far-ranging indeed. It stretches over the fields of amino acids, proteins, and enzymes; aromatic and aliphatic hydrocarbons, including carotenoids as well as synthetic polyenes, cumulenes, highly acidic hydrocarbons, and radicals; vitamins, growth-factors, and inhibitors; such heterocyclics as the flavins, tetrazolium salts, and the newly discovered verdazyls and other nitrogen radicals; natural quinones; alkaloids; gangliosides; and glycosides and sugars of manifold descriptions. Inspired by the great paragon, J. H. van't Hoff, Kuhn was particularly attracted by problems of stereoisomerism, and it was in this area that he made some of his early contributions of major significance. He was equally fascinated by the relations between structure and physical properties, especially light absorption. Much of his research was prompted by an almost playful joy in color phenomena, whether these occurred in Nature or in the test tube; and close collaboration with his physicist colleagues in the Heidelberg institute, Professor K. W. Hausser and his wife, Isolde Hausser, brought forth important contributions to spectroscopy and photochemistry. In whatever field he embarked upon exploration, he applied himself unreservedly; but his steadiest love, yielding the highest rewards over all, although some bitter disappointments too, was the interplay between structural organic chemistry and biological functions. Guided by a profound knowledge of principles and a fantastic memory for details, cognizant of all current trends in science, often stimulated by artistic intuition, Richard Kuhn moved at ease in orbits traversing nearly all of chemistry and encompassing the border precincts of physics, biology, and medicine. A large number of students and postdoctoral assistants flocked to him, each contributing with enthusiasm his share to the team's prolific work, and from his school emerged many who later attained professorships and other creative positions throughout the world. T. Wagner-Jauregg, A. Wassermann, A. Winterstein, H. Brockmann, E. Lederer, C. Grundmann, E. F. Möller, H. Rudy, L. Birkofer, F. Weygand, P. Desnuelle,

N. A. Sörensen, F. Giral, G. Wendt, O. Westphal, T. Wieland, and D. Jerchel, among many others, collaborated during the first great period of Kuhn's productivity, which extended into the early forties and culminated in the award of the Nobel prize in chemistry[3] for 1938. H. Beinert, H. J. Bielig, G. Quadbeck, F. Zilliken, H. A. Staab, F. Drawert, Herb. Fischer, and others, joined later. With exceptions to be mentioned, the work with these associates was largely outside the field of carbohydrate chemistry and cannot be given proper appreciation in these pages.[4]

By early 1927, at about the time of his moving to Zürich at the age of twenty-six, Richard Kuhn had sixty publications to his credit, being co-author with Willstätter of eight, and single or senior author of the rest. That work comprised extensive research on carbohydrate enzyme specificity, mainly regarding the action of sucrases, maltase, raffinase, amylases, and emulsin upon various substrates. It was recognized that yeast invertase contains two separable enzymes which can hydrolyze sucrose; they are now referred to as α-D-glucopyranosidase and β-D-fructofuranosidase. Important contributions were made on the structure of starch, turanose, melezitose, and amygdalin, and the kinetics of sugar mutarotation and of permanganate oxidation were studied (with H. Sobotka, G. E. von Grundherr, and others). Keenly interested in general problems of stereochemistry, Kuhn investigated the mechanism of the Walden inversion, the stereoisomerisms in chloromalic acid and cyclopropanedicarboxylic acid, and, particularly, the molecular asymmetry that causes rotational isomerism in *ortho*-substituted biphenyl derivatives (with F. Ebel, T. Wagner-Jauregg, and O. Albrecht). He later coined the term "atropisomerism" for stereoisomerism that is based on restricted rotation about single bonds, clearly realizing the stereochemical significance of this feature at a time when the concept of conformation had not yet been established.

Following his moves to Zürich and Heidelberg, Kuhn's interest in carbohydrates was temporarily overshadowed by his rapidly developing polyene work. However, sugar studies were resumed in connection with the structural elucidation and synthesis of riboflavine, which had been isolated in 1933 in collaboration with P. György and T. Wagner-Jauregg. Riboflavine [vitamin B_2, 6,7-dimethyl-9-(D-*ribo*-

(3) The citation honored Richard Kuhn's work on carotenoids and vitamins. Like other German Nobel laureates in that era, he was forced by the National Socialist regime to decline the prize, but, after the war, the Nobel Committee ruled the refusal null and void, and the honors were conferred.

(4) For an excellent account, see O. Westphal, *Angew. Chem.*, **80**, 501 (1968).

2,3,4,5-tetrahydroxypentyl)isoalloxazine] was synthesized, starting from D-ribose and 3,4-dimethylaniline (with F. Weygand); the 5′-phosphate (flavine mononucleotide) was then prepared, and combined with the protein moiety of Warburg's yellow enzyme, in what was the first partial synthesis of an active enzyme (1934-1936, with H. Rudy). Many glycosylamines and aminodeoxyalditols were prepared, and their reactions were studied concomitant with, and following, these achievements; one of the results was the realization (with A. Dansi) that the nonhydrolyzable, strongly reducing products that arise from aldosylamines under certain conditions are 1-amino-1-deoxyketoses. The now-familiar name "Amadori rearrangement" was proposed for this transformation by Kuhn and Weygand; actively participating in these investigations (1936-1938) were R. Ströbele and L. Birkofer. Two decades later, Kuhn was to return to the study of the Amadori rearrangement (with F. Krüger and Annemarie Seeliger), making use of it, for instance, in a simple synthesis of lactulose. Other research during the earlier period led to elucidation of the structure of picrocrocin, an alkali-labile glycoside constituting the bitter principle of saffron.

In the 1940's, Richard Kuhn's interest in carbohydrates was sustained, and it gradually rose to become his dominant (though by no means exclusive) preoccupation during the last fifteen years of his life, a period that was also marked by a second peak of his immense productivity. He had the good fortune of being able to rely on three trusted and extremely competent associates who served with him faithfully through three decades until his death, doing carbohydrate research with dedication and providing an element of continuity in ever-changing complements of students and assistants. They were Drs. Irmentraut Löw and Adeline Gauhe, and Mr. Heinrich Trischmann. The direction of work first turned toward the isolation and biological evaluation of plant glycosides. Flavonol glycosides were identified, and aglycons (rhamnetin and rhamnazin) were synthesized. A large area of study then opened up in steroid-related alkaloid glycosides that occur in the leaves of potato and tomato plants and other *Solanum* species. These attracted Kuhn's interest in connection with phenomena of biological resistance which, in their diversified manifestations, had always intrigued him. Why are certain *Solanaceae* resistant against the potato beetle (*Leptinotarsa decemlineata* Say), whereas others are beset by this pest, which has blighted many a potato crop? It was discovered that certain alkaloid glycosides, namely, tomatine from tomato leaves, demissine from *Solanum demissum*, and leptine from *Solanum chacoense* (both of which are wild potatoes, native to Central and South America), act as beetle repellents, rendering the leaves resistant, whereas the long-known solanine and the newly isolated chaconine, which are present in the common potato plant, are inactive. The latter two glycosides were found to contain the same aglycon, solanidine, but to differ in their branched, trisaccharidic sugar moieties. Solatriose was demonstrated to be O-α-L-rhamnopyranosyl-(1 → 2)-[O-β-D-glucopyranosyl-(1 → 3)]-D-galactose, and chacotriose was shown to be 2,4-di-O-α-L-rhamnopyranosyl-D-glucose. Tomatine and demissine were revealed to differ in their aglycons, but to contain the same sugar moiety, called lycotetraose. The latter was established to be O-β-D-xylopyranosyl-(1 →3)-[O-β-D-glucopyranosyl-(1 → 2)]-O-β-D-glucopyranosyl-(1 → 4)-D-galactose. Two highly active leptines were found to resemble solanine and chaconine, respectively, in regard to their sugar units; the activity was associated with an ester acetyl group in the aglycon (work with I. Löw and, in part, H. Trischmann and A. Gauhe). Considerable improvements in the technique of sugar methylation were elaborated in connection with these studies, and have since enjoyed frequent application.

In 1952, problems of biological resistance prompted Richard Kuhn to return to research on milk. It had become apparent that human milk, as opposed to cow's milk, enhances resistance in infants against bacterial and viral infections. Collaboration with P. György, now at Philadelphia, was resumed some twenty years after their joint investigations on lactoflavine, and a large-scale program concerning the physiology and chemistry of milk was launched. The growth-promoting activity of human milk for *Lactobacillus bifidus*, the normal intestinal flora that is beneficial to the baby's health, was recognized to reside in the carbohydrate fraction; part of it is due to nitrogen-containing oligosaccharides. In the transatlantic co-operation that developed, microbiological aspects were pursued in Philadelphia, while the chemical studies mainly took place in Heidelberg. Hundreds of gallons of human milk were procured—no mean feat in research logistics—and the carbohydrate fractions were passed through batteries of chromatography columns. With A. Gauhe and H. H. Baer, about a dozen native oligosaccharides were isolated, and many additional ones were obtained by partial hydrolyses in the course of subsequent structural work. Occupying a central position among these sugars, "lacto-N-tetraose" was shown to be O-β-D-galactopyranosyl-(1 → 3)-O-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1 → 3)-O-β-D-galactopyranosyl-(1 → 4)-α-D-glucose. Several penta- and hexasaccharides proved to be derived from the tetraose by attachment of

L-fucose residues and *N*-acetylneuraminic acid residues at various positions. Furthermore, trisaccharides and tetrasaccharides composed of lactose plus one or two L-fucose residues, and of lactose plus one or two *N*-acetylneuraminic acid residues were found to occur in human milk.[5] In elucidating the oligosaccharide structures, considerable attention was paid to alkaline degradation and its dependence on the type of linkage, especially in conjunction with the Morgan–Elson color reaction for *N*-acetylhexosamines. The mechanism of the latter reaction was studied (with G. Krüger) and found to involve the formation of 3-acetamidofuran derivatives as chromogens. Insights thus gained have contributed a great deal to later structural work by others in such important areas as blood-group substances, whose carbohydrate components resemble the milk oligosaccharides in many ways. Several of the di- and tri-saccharides described for the first time by Kuhn and his coworkers as hydrolytic fragments of higher saccharides have since been encountered as building units elsewhere in Nature.

In concurrent investigations with R. Brossmer, crystalline 3′-*O*-(*N*-acetylneuraminyl)lactose was isolated from cow colostrum and demonstrated to be a substrate for influenza virus enzyme and for the "receptor-destroying enzyme" of *Vibrio cholerae*. The structure of *N*-acetylneuraminic acid, then still a matter of contention, was clarified by chemical degradation, and the configuration at C-4 that had remained unknown was established. Finally, the acid was synthesized in good yield (with G. Baschang).

Another extensive program, begun in the early sixties, was directed at the chemical exploration of the brain gangliosides. These compounds, which are glycolipids consisting of fatty acid, sphingosine, and an oligosaccharide moiety, are presumed to play an important role in the physiology of nervous tissue. With H. Wiegandt and H. Egge, several gangliosides were structurally elucidated. The carbohydrate parts attached were demonstrated to contain, as the central core, a tetrasaccharide ("ganglio-*N*-tetraose"), namely, *O*-β-D-galactopyranosyl-(1 → 3)-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1 → 4)-*O*-β-D-galactopyranosyl-(1 → 4)-D-glucose, to which are bound *N*-acetylneuraminic acid residues in various numbers and at various sites. The close analogy to the milk oligosaccharides is obvious, although 2-amino-2-deoxy-D-galactose takes the place of 2-amino-2-deoxy-D-glucose, and L-fucose is absent.

Synthetic work included the preparation of several disaccharides for comparative and systematic purposes. Thus, 2-acetamido-2-deoxy-

(5) See F. Zilliken and M. W. Whitehouse, *Advan. Carbohyd. Chem.*, 13, 237 (1958).

lactose, 2-acetamido-2-deoxyallolactose, 3-*O*-β-D-galactopyranosyl-D-glucose, and 3-*O*-β-D-galactopyranosyl-D-fructose, among others, were synthesized chemically (with H. H. Baer and W. Kirschenlohr). However, the emphasis rested on the synthesis of monosaccharidic amino sugars. The method of catalytic hemihydrogenation of α-aminonitriles, first elaborated with W. Kirschenlohr, and then investigated further and comprehensively employed by G. Baschang, Waltraut Bister, H. Fischer, J. C. Jochims, and D. Weiser, proved extremely versatile in the synthesis of 2-amino-2-deoxyaldoses (1956–1961). Aldoses were condensed with hydrogen cyanide and an amine (aniline, benzylamine, or ammonia) according to the pattern of Emil Fischer's synthesis of 2-amino-2-deoxy-D-glucose, but the α-aminonitriles so obtained were then hydrogenated catalytically, the reduction being arrested at the aldehyde stage. (All eight 2-amino-2-deoxy-D-hexoses and many other amino sugars, such as 2-amino-2-deoxypentoses, 2-amino-2-deoxytetroses, and 6-deoxy derivatives, have thus been prepared, some for the first time.) The Kuhn synthesis (the first) of 2-amino-2-deoxy-D-arabinose still stands as the best method for obtaining this sugar. In addition, extremely interesting studies concerning epimerizations, tautomerizations, rearrangements, and dehydrations in aminodeoxyaldononitriles, aminoaldonic acids, and amino sugars were performed, and various biochemical experiments relating to amino sugar metabolism were carried out. With close to a hundred articles published in the period 1952–1967 on nitrogen-containing carbohydrates alone, Richard Kuhn certainly ranks high among those who have made the most significant contributions to this field. In between the researches sketched above, numerous reactions in the general chemistry of carbohydrates were studied. As one example may be mentioned an investigation with W. Bister on the peroxy acid oxidation of sugar dithioacetals to mono- and bis-sulfoxides and on the fission of these oxidation products.

Richard Kuhn's extraordinary personality could not fail to impress anyone who came in contact with him. Time and time again, his coworkers would stand in amazement at his ingenious deductions and often unexpected suggestions, which flowed from an inexhaustible fund of knowledge and from analogies that were not readily available or obvious to his lieutenants. Spellbound lecture audiences would hear his resonant, melodious voice expound problems and results of research, forcefully and with didactic discipline, often revealing striking interrelations between matters seemingly apart, and always heading for a finale that would open grand vistas of potential future developments. Nevertheless, however synoptic his views, it was not at all beneath Richard Kuhn to attend painstakingly to small details