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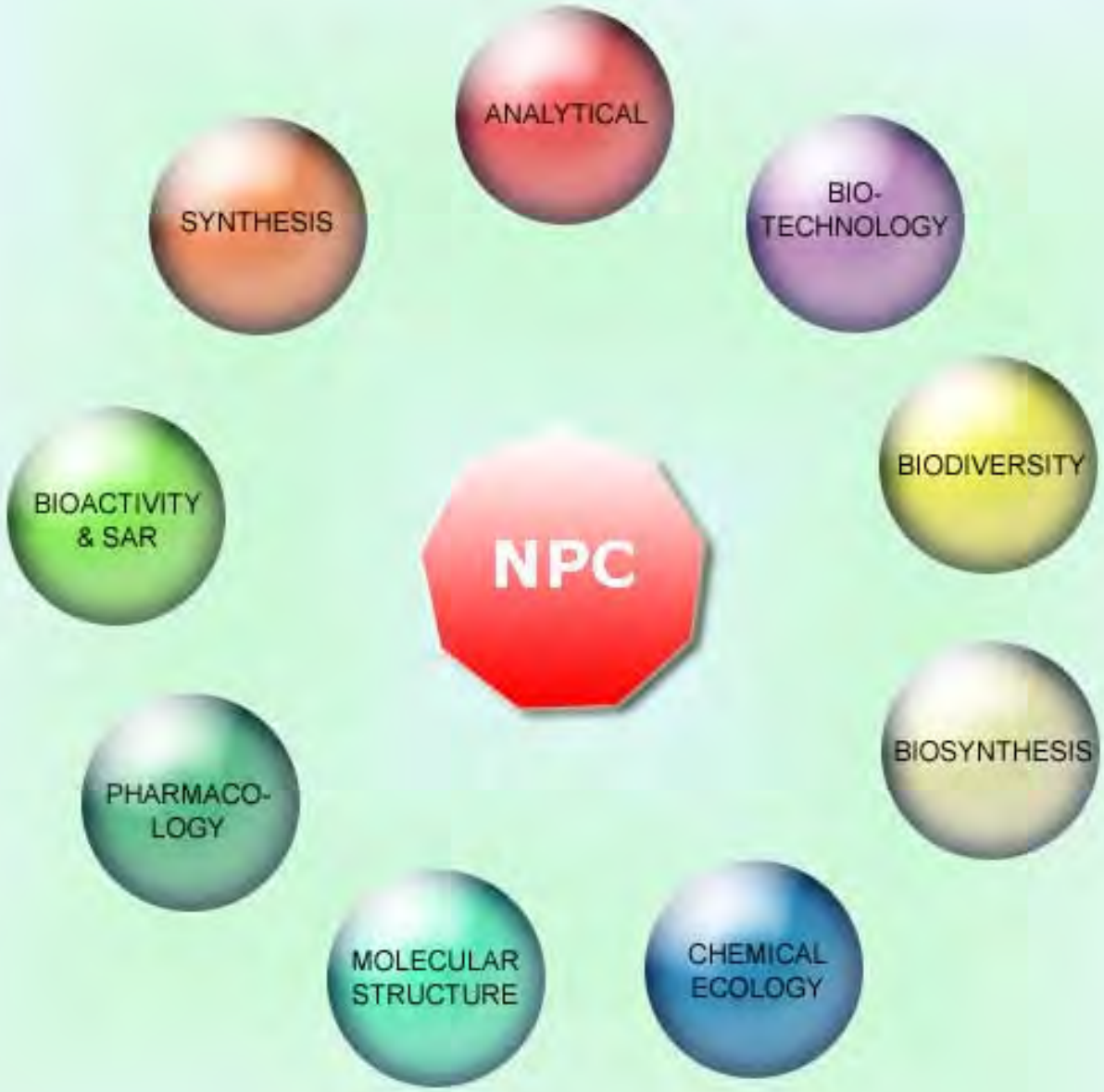

This Issue is Dedicated to
Professor Tom J. Mabry
on the Occasion of his 75th Birthday

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Tom J. Mabry's Natural Products Chemistry Program: 1960-2007

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This paper is dedicated to Professor Tom J. Mabry for his 75th birthday.

This paper presents an overview of Dr. Mabry's accomplishments in his career as a natural product chemist, first at the University of Zürich as a post-doctoral fellow, and from 1962, as a faculty member at the University of Texas at Austin in the Department of Botany until the late 1990s, when the Biological Sciences programs at UT-Austin were completely reorganized. From then until his retirement in 2006, he was a member of the Molecular Cell and Developmental Biology faculty.

Keywords: Tom J. Mabry, University of Texas at Austin, Natural Products Chemistry.

This issue of Natural Product Communications is dedicated to the 75th birthday of Tom J. Mabry, Professor Emeritus at the University of Texas at Austin. For this paper, I outline Dr Mabry's outstanding achievements in the field of natural products chemistry, and I add Dr. Mabry as second author in appreciation of his many comments and contributions. As his last Ph.D. student, it is my special honor to describe the personal and professional impact Dr. Mabry has made on my life, a sentiment that is shared by many, if not all of his students, post-doctoral fellows and colleagues over the last 40 years as a Professor at UT-Austin. To prepare this report of his accomplishments, I pursued many of his publications (nearly 700!), including 15 books and several dozen chapters, as well as some of his students' dissertations and theses. In addition to reviewing these written works, I also summarize Dr. Mabry's accounts of several of his major projects, beginning with his Ph.D. studies on the coenzymatic activity of Vitamin C and his post-doctoral investigations marking the discovery of a new class of plant pigments found initially in beets, the betalains, which proved significant for the plant sciences and thus for his career at UT-Austin. In addition, I interviewed a few of his more than 70 MS and Ph.D. students and about ten of his hundreds of post doctoral fellows, as well as several of his faculty colleagues.

Although Dr. Mabry modestly credits his career success to "the luck of pursuing the right projects with the right people at the right time", when I began to review his many accomplishments, awards and memberships, it was clear that most of his success came from his own intense efforts. Dr. Mabry was instrumental in organizing the Phytochemical Society of North America in 1966 and early in his career, Prof. T.W. Goodwin, a distinguished biochemist in England, praised Mabry as the "Father of Modern Phytochemistry in the United States". Mabry has received numerous awards, including a Guggenheim Fellowship for a year at the University of Freiburg, Germany, the Alexander von Humboldt Senior Scientist Award for research with Prof. Dietmar Behnke at the University of Heidelberg, Germany; the American Chemical Society Award for the "Application of Chemistry to Food and Agriculture"; the "Pergamon Phytochemistry Prize"; the UT-Austin Graduate School's "Outstanding Doctoral Teaching Award"; and the American Society of Pharmacognosy's "Research Achievement Award". It

would take much more than this paper to describe all of Dr. Mabry's many contributions to natural products chemistry, thus, I will provide just a few examples of the scope and breadth of his work while highlighting his extraordinary abilities as a teacher and scientist.

Dr. Mabry's 1956-1960 Ph.D. studies expanded on an earlier finding that L-ascorbic acid (Vitamin C) had unusually high coenzymatic properties for the hydrolysis of mustard oil glucosides, while D-ascorbic acid, which has no Vitamin C activity, showed no coenzymatic activity for the hydrolysis of these same glycosides. Since many analogs of L-ascorbic acid had been tested in the 1930s in Guinea pigs and were found to exhibit either low or no Vitamin C activity, Mabry synthesized the same analogs and established that they each had low or no activity for the hydrolysis of the glycosides, that is, the same pattern they had exhibited for Vitamin C activity (Figure 1). His findings suggest that the Vitamin C activity of L-ascorbic acid is related to its coenzymatic properties and not to its well-established antioxidant potential [see discussions of these findings in 1, 2]. Dr. Mabry strongly encourages further investigations to determine which reactions in humans, if any, involve L-ascorbate as a coenzyme in its role as Vitamin C. (Mabry suspects the coenzyme activities of L-ascorbic acid could be involved with the synthesis of new tissue to replace that degraded by colds, aging and, in earlier times, in Vitamin C deficiency diseases such as scurvy).

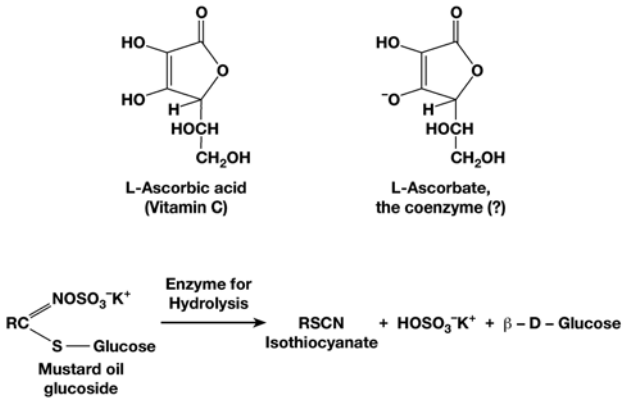

Figure 1: The rate of hydrolysis of mustard oil glucosides is markedly increased by L-ascorbic acid (Vitamin C), but not by D-ascorbic acid, which has no vitamin activity. Synthetic analogs of L-ascorbic acid exhibited comparable patterns of Vitamin C and coenzymatic activities.

After receiving his Ph.D. in Chemistry in 1960 from Rice University, he joined the group of Professor Andre Dreiding (a specialist for reaction mechanisms) in the Organic Chemistry Institute, University of Zürich, Switzerland. He was assigned to tackle Dreiding's only plant project, namely to determine the structure of the red beet pigment, betanin, that was thought to be a member of the well-known and widespread pigments, the anthocyanins (roses, red wine, etc.); however, it was referred to as a "nitrogenous anthocyanin" because both of the breakdown products from betanin contained nitrogen. Dr. Mabry recognized that previous investigators in Dreiding's labs had used rather harsh conditions that degraded the beet pigment to the nitrogenous breakdown products. Therefore, he employed very mild procedures for derivatizing betanidin, the aglycone of betanin: for example, methylation with diazomethane in ether at neutral pH and room temperature. Using variations of such mild procedures Mabry was able to isolate several derivatives of betanidin that contained all the carbon, oxygen and nitrogen atoms found in this aglycone of betanin; he named these derivatives neobetanidins. In collaboration with Hugo Wyler and others in Dreiding's group, Mabry quickly established the structures of the neobetanidins, as well as betanidin and betanin [3, 4]. These findings startled the plant world because the new structures were not related to those for anthocyanins; thus, a new class of pigments, the "betalains" was recognized (Figure 2) [the name was selected by Mabry and Dreiding and published by them in 1968 [5].

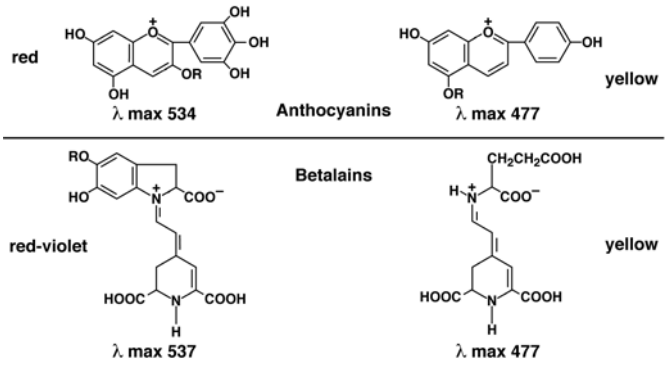

Figure 2: In the late 1960s, Mabry and Dreiding recognized the betalains as a new class of pigments that are found in nine plant families; these families produce none of the well-known and widely distributed plant pigments, the anthocyanins.

In 1962, Dr. Mabry accepted a position in the plant biology program at the University of Texas at Austin to organize a major natural products chemistry program in the Department of Botany. Professor B. L. Turner (now Emeritus), a distinguished plant systematist at UT-Austin, and his plant physiologist colleague, the late Dr. Ralph Alston, were instrumental in recruiting Dr. Mabry from the

University of Zürich (see Figure 3). With the support of Turner and Alston, Mabry assembled a group of truly outstanding chemistry and biochemistry post-doctoral fellows and many bright and motivated botany graduate students who wanted to learn all they could about chemical techniques for studying plants (Figure 4). Moreover, he was able to obtain funding for the new research programs from NSF, NIH, USDA and many foundations, including, especially, the Robert A. Welch Foundation in Houston, which still today supports his program; he also obtained special funds for NMR, MS, UV and chromatographic equipment.

Prior to 1962, botanists at UT-Austin had observed that when extracts of *Baptisia* (family Leguminosae) and several other genera were analyzed by two-dimensional paper chromatography and then examined under UV light, the patterns of brightly colored flavonoid "spots" were often reliable markers for species identifications and for recognizing hybrids (Figure 3) [6, 7]. Since it was clear that having actual chemical structures for each "spot" would enormously increase the reliability of using these data for plant systematics, Mabry's initial goal was to characterize structurally the flavonoids in *Baptisia* species. Thus, a leading biochemical systematic research program was established in Mabry's lab, one that would continue to produce many new natural products for systematics, evolutionary studies and medicine for the next 40 years.

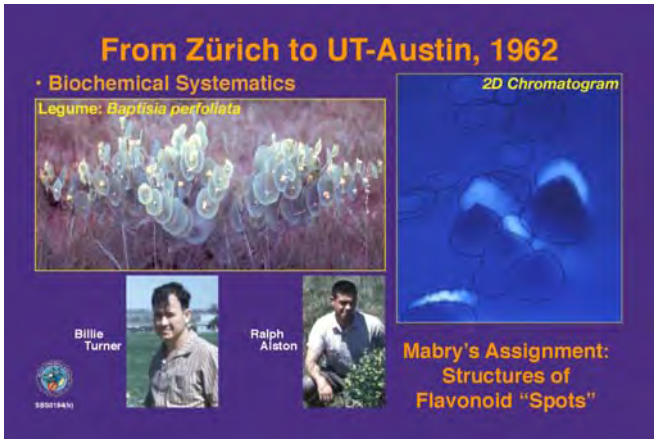

Figure 3: The biochemical systematic investigations underway at UT-Austin in 1962 utilized 2D paper chromatography to distinguish species and recognize hybrids in the legume genus *Baptisia*, as well as other taxa. Mabry's phytochemistry laboratory was charged with providing structures for the florescent flavonoid "spots" detected when the chromatograms were viewed under UV light.

Figure 4: Dr. Mabry (center) with coworkers in the late 1960's, including his future wife Helga Fischer (center right), a Chemical Technician from Germany. Coworkers, clockwise from top left: Dr. Ken Markham, Al Wohlpart*, Gene Miller*, Julis "Bud" Kroschewsky*, Helga, Hanspeter Rüesch (Chem. Tech), Dr. Klaus Fischer, Dr. Michael Thomas, Chistina Chang*; * Ph.D. students.

By 1970, Dr. Mabry and coworkers had documented the flavonoid patterns from an enormous number of plants from around the world. In addition to publishing many papers on their findings, they produced what quickly became the standard text for flavonoid studies, the book titled "The Systematic Identification of Flavonoids" [8]. This volume, which is still used today, includes 1000s of interpreted UV and NMR spectra of members of different classes of flavonoid aglycones and glycosides. Moreover, the book presents details of how to best extract and purify flavonoids from plants in a user-friendly format that allows botanists with little or no chemistry training to identify flavonoids and other phenolic compounds using spectral techniques (Figure 5).

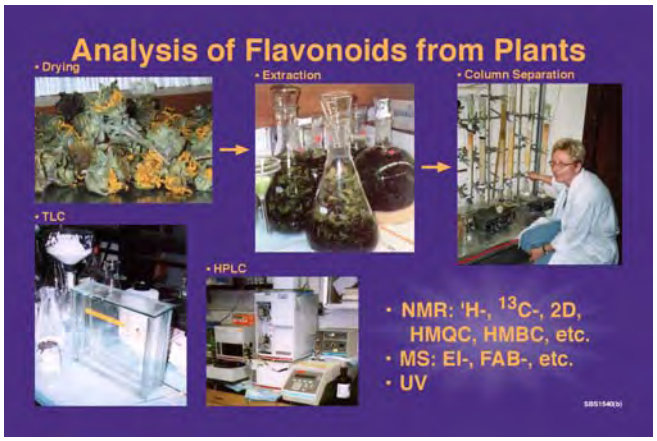

Figure 5: Some of the analysis procedures developed for flavonoids in Mabry's lab.

Today, plant systematics is dominated by DNA studies; nevertheless, some plant relationships are still better understood by combining chemical and molecular data; for example, in the 1960-1970s, with the help of the plant systematists at UT-Austin,

Mabry and coworkers established that betalains were restricted to some nine plant families in the Order Caryophyllales, some aligned solidly there for the first time (e.g. the Cactaceae). Mabry's group later used DNA studies to confirm the close evolutionary relationship of all these families; however, these nine betalain families contained no anthocyanins (pigments that are in found over 95% of flowering plants) and somewhat to Mabry's surprise, two other families that clearly belong in the Order Caryophyllales, the Caryophylaceae and Molugenaceae, contained only anthocyanins and no betalains (Figure 6) [9, 10, 11, 12, 13, 14, 15, 16 and many other Mabry papers].

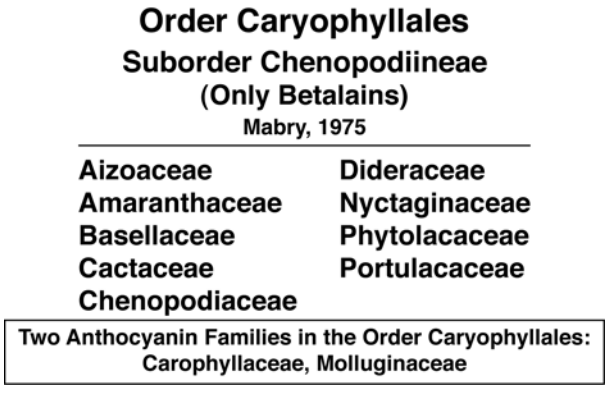

Figure 6: In higher plants, betalains were found to occur in nine plant families in the Order Caryophyllales, which also houses two families that have only anthocyanins, that is, no betalains.

This example illustrates both the usefulness and the limitations of chemical data in understanding plant evolutionary relationships. Mabry's group found that in addition to systematics, natural products chemistry can often aid in resolving many plant biology questions, such as determining the survival potential of plants in particular ecosystems [17, 18, 19 and many other Mabry papers].

Also in the 1960s-1970s, Mabry expanded his plant chemistry program to cover many other classes of natural products, for example, different types of phenolic compounds, as well as sesquiterpene lactones and diterpenes, studies that resulted in many papers, as well as two data-filled volumes [20, 21]. Other groups of natural products investigated include all other classes of terpenes, as well as nonprotein amino acids, azoxyglycosides, some alkaloids and many others (many Mabry papers). Mabry also investigated the chemistry of numerous disjunct taxa, including populations of some species found in North and South America [22, 23, 24, 25], as well as the chemistry of many arid land plants [26, 27, 28, 29, 30, 31]. In addition, his group tested many of the new natural products for a wide range of biological properties including their antifeedant, antibiotic, anticancer, free radical scavenging, anti-inflammatory, hepatoprotective and other activities to determine some of their roles in evolution as well as their potential for medical uses.

Dr. Mabry always encouraged students who presented a good research plan to tackle projects of their own interest, even when outside his areas of specialization. For example, Ph.D. student Maureen Bonness, who, in the 1980s, at Dr. Mabry's suggestion, initiated investigations of betalains in pokeweed (*Phytolacca americana*, family Phytolacaceae). However, while reading literature on this plant, Bonness learned that this very same species contains a special class of proteins known as "PAP" for "pokeweed antiviral protein" (the more general name is "RIP" for "ribosome inactivating protein"). So Bonness decided to investigate the antiviral proteins in *Phytolacca americana* and quickly confirmed that PAP can inactivate ribosomes inside the *Phytolacca* cells, preventing any "PAP-invaded" cells from replicating [32]. Bonness, with other coworkers [e.g. 33], established that PAP is in an active form in the cell walls of this *Phytolacca* species, and, in addition, she found that when a virus enters through the cell wall, PAP also enters and that the PAP quickly inactivates the ribosomes, which not

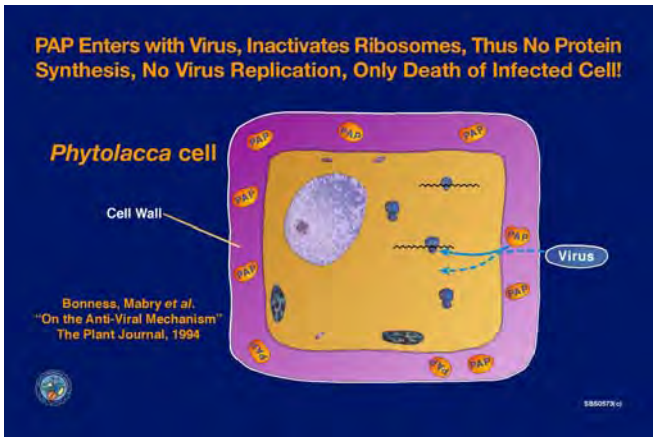

Figure 7: The mechanism by which the antiviral proteins (PAP) that occur in the cell walls of *Phytolacca americana* protect these plants from viral infections; PAP "piggybacks" into a *Phytolacca* cell when a virus enters and then kills that single infected cell, thus preventing spread of the virus.

only causes the death of these PAP-invaded cells but also prevents replication of the virus, keeping the remainder of the plant free of the virus (Figure 7) [32]. Other laboratories have reported that when the gene for PAP is inserted into another plant, such as those for crops, these genetically modified plants are protected from viruses; unfortunately, the next generations of these genetically modified plants usually eliminate the gene for PAP. Also methods are currently being developed in European labs and elsewhere to use PAP to protect human cells against the HIV virus and some cancer viruses. Mabry hopes these remarkable antiviral proteins will continue to be investigated for both agricultural and medical uses.

Bonness's curiosity and keen observation skills also helped to establish another major project in the Mabry lab. When she happened to notice in a class project that fungus-contaminated cell cultures of the cactus *Cephalocerus senilis* (old man cactus) turned red, she quickly established that the red pigments were not betalains. This finding lead to further investigations by others in Mabry's group, namely Paul Paré and coworkers, who found that the new compounds in these cultures were being elicited by chitin (an elicitor of protective compounds for plants that was known to occur in fungi). Paré and others in the Mabry lab established that most of the elicited compounds belonged to a new class of 4′-deoxyflavonoids, including an unusual new aurone with high antibiotic properties (Figure 8) [34, 35, 36, 37, 38, 39]. Cultures of another distantly related cactus, *Opuntia microdasys*, also turned red when treated with chitin and preliminary analysis showed a similar pattern of 4′-deoxyflavonoids [40]. Mabry

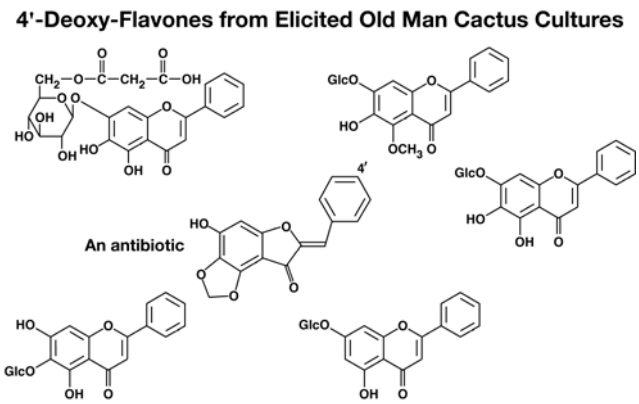

Figure 8: Fungus-infected cactus cell cultures produced unique 4′-deoxyflavonoids as a result of the action of the elicitor chitin, a fungal component.

believes that treating cultures of other cacti, as well as plants from other families, with elicitors such as chitin could produce many more new and important compounds.

In the late 1980s Dr. Len Kurland, a distinguished ethnobotanist who spent his early years at NIH before joining the Mayo Clinic in Rochester, Minnesota, presented a new project to Mabry. Kurland pointed out that a terrible neurodisease occurring in members of the Chamorro tribe on the island of Guam exhibited symptoms of ALS, Parkinson's dementia and Alzheimer's disease and was over 100 times more prevalent on Guam than such neurodiseases elsewhere. After years of studying this disease and finding no other cause for it, Kurland finally focused on a possible dietary "culprit." Kurland explained to Mabry that the Chamorros traditionally consumed seeds of the Guam cycad (*Cycas micronesia*) leading him and others to suspect that these seeds might contain a neurotoxin. However, other scientists determined that there were only very small quantities of the "suspect" compound, β-methylaminoalanine (BMAA), in the thoroughly washed cycad flour being used for tortillas by the Chamorros. Kurland persuaded Mabry to reinvestigate whether cycads and BMAA (or other compounds) were involved in this Guam neurodisease. Delia Brownson, an excellent Ph.D. student, initiated the research by searching literature reports on the project, and learned that neurodiseases were, in many cases, caused by channels in human brain cells opening improperly, allowing too much calcium into the cells, which then caused the death of some of the cells, leading to neurodiseases. She also learned that BMAA, the Guam cycad compound, complexes with CO_2 in solutions of BMAA and CO_2 at physiological pHs to

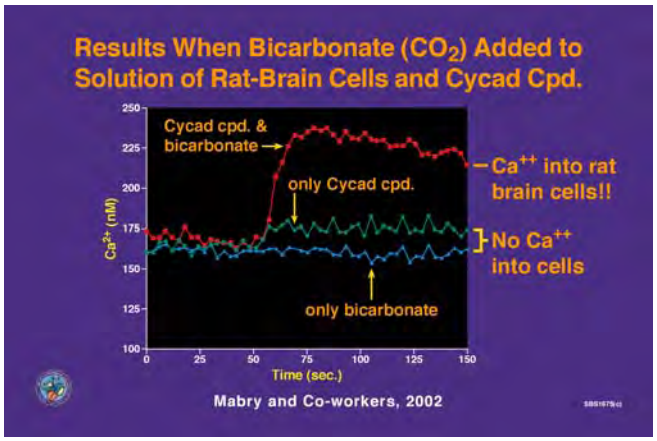

Figure 9: Mabry's lab showed that the cycad compound β-methylaminoalanine (BMAA) could increase Ca^{2+} levels in rat brain cells, but only in the presence of bicarbonate, implicating the carbamate of BMAA as the cause of ALS-PDC.

form an unstable compound called a carbamate. This unstable carbamate (present in about 10% yield in an equilibrium reaction in these solutions) has a structure remarkably similar to the neurotransmitter glutamic acid, one of the very compounds that our brains use to properly and regularly manipulate calcium channels. Suspecting involvement of the carbamate of BMAA, Brownson first tested BMAA alone in solutions of fresh rat brain cells and found that, as expected, no calcium entered the cells. Next, she added sodium bicarbonate (a source of CO_2) to the same solution of BMAA and rat brain cells, and, sure enough, the channels opened and calcium entered the rat brain cells (Figures 9, 10) [41,42]. These results suggest that the carbamate of BMAA may be the cause of the neurodisease that afflicted so many Chamorros on Guam.

Increasing the significance of Brownson's findings were reports in this decade by Paul Cox and his coworkers (earlier based at the Institute of Ethnobotany in Kalaheo, Hawaii, but now associated with Brigham Young University, Provo, Utah) who proposed what Mabry believes is the probable route by which BMAA enters the brains of the Chamorros: Cox's group established that Guam bats accumulate BMAA in their bodies by eating the cycad seeds and that the Chamorros feast on these BMAA-rich bats [43 and later publications]!

Although this theory has received some skepticism, there is other evidence that points to the dietary consumption of bats as the likely route of BMAA into the brains of the Chamorros, namely, when in the early 1970s the Guam bats were

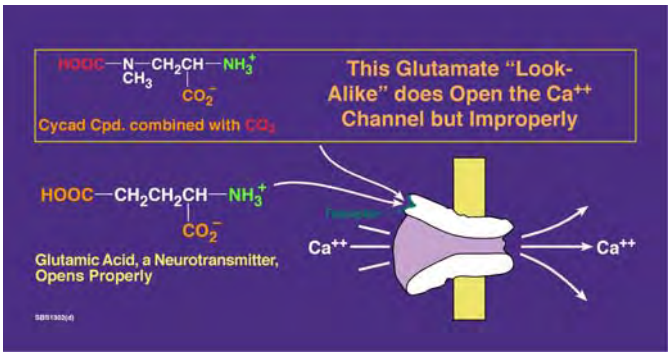

Figure 10: BMAA, the cycad compound, can complex with CO_2 to give a carbamate. Mabry's group showed that this carbamate allows calcium to enter rat brain cells, presumably by binding to the glutamate receptor protein and opening the calcium channels. Mabry believes this carbamate may be the cause of ALS-PDC.

classified as an endangered species and hunting of them was outlawed, no new cases of the neurodisease were reported on Guam!! For obvious reasons, Dr. Mabry considers that it is extremely urgent for researchers to finally determine if compounds such as the carbamate of BMAA can indeed cause neurodiseases by binding to receptor proteins for neurotransmitters and improperly opening the calcium channels.

Now I mention my own Ph.D. studies that are being supervised by Dr. Mabry. My dissertation research involves both phytochemical and chemosystematic studies of members of one of the largest and most diverse plant families in the world, the Sunflowers. The genus *Silphium* L. (Asteraceae) consists of eleven species native to North America, distributed primarily in the eastern United States and extending into southeastern Canada [44]. I became interested in this genus because extracts of several *Silphium* species were widely used for herbal medicines by central and southeastern Native American tribes [45], yet there have been few attempts to correlate phytochemical findings with their traditional herbal uses. One previous study led to the isolation and characterization of eight major triterpene glycosides from *Silphium perfoliatium* (Figure 11) [46]. Also, a mixture of these triterpene saponins from *S. perfoliatum* showed blood cholesterol-lowering activity, as well as fungicidal properties [47, 48].

Thus, in an effort to further characterize triterpene glycosides from *Silphium* and determine some of their medical importance, I initiated an analysis of saponins in all species of *Silphium*, some of which contain up to nine triterpene saponins with new aglycones.

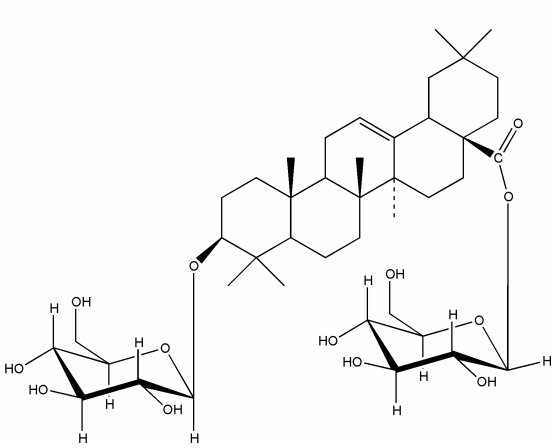

Figure 11: Silphioside B, one of the 8 major triterpene saponins previously isolated from *Silphium perfoliatum* [46].

Since the investigation of saponins was an entirely new area of research in the Mabry lab, the first step in my dissertation project was to gain instrumentation training and learn isolation techniques to characterize saponins. With Dr. Mabry's support and encouragement, I established connections with a number of leaders in the field of saponin chemistry, particularly, in the laboratory of Professor Wieslaw Oleszek in Pulawy, Poland where I learned procedures essential for the characterization of saponins. In addition, I gained skills for interpreting complex NMR spectra of my compounds from Dr. Ben Shoulders, Professor of Chemistry at UT-Austin and from Professor Sonia Piacente, a NMR specialist for saponins at the University of Salerno, Italy. Once the major saponins from *Silphium* were characterized, the cytotoxic activities of the isolated compounds were tested against human breast cancer cell lines in collaboration with Dr. Su Dharmawardhane, Universidad Central del Caribe School of Medicine, Puerto Rico. The results indicate that one of the new saponins isolated from *Silphium radula* decreased proliferation of breast cancer cells in a statistically significant manner. Finally, I was able to establish an LC-MS detection method for saponins in *Silphium* in order to identify the major saponins in all *Silphium* species with the help of Dr. Paul Paré and coworkers at Texas Tech University, Lubbock, Texas. My analyses of the many new and known triterpene saponins in all eleven species of *Silphium*, as well as my findings for their systematic and medicinal value, will be complete and published in the 2007-2008 academic year.

During Dr. Mabry's retirement celebration in October 2005 at UT-Austin, there were three major speakers,

Figure 12: Dr. Mabry and his last Ph.D. student Lalita Calabria (senior author of this paper) in Lublin, Poland, June 2006, at the 5th International Symposium on Chromatography of Natural Products

all former students of Dr. Mabry: Dr. Paul Paré and Dr. Jonathan Gershenzon, as well as Dr. Barbara Timmermann, Chair of the Department of Medicinal Chemistry and Distinguished Professor of Medicinal Chemistry, School of Pharmacy, University of Kansas. Dr. Timmermann mentioned in her lecture that once when Dr. Mabry had helped her resolve a difficult issue, she asked what she could do for him, he responded "pass it on," meaning that in her role as a professor, she must not only educate and train students with all her knowledge and techniques for this field but also help them develop essential people-to-people skills. Moreover, she must inspire and support students through their challenging times so they can achieve their goals and dreams. Later in the celebration, Dr. Jim Gill (M.D.) pointed out that he might not have reached his goal of becoming a medical doctor without the opportunity to spend his undergraduate years in Mabry's lab where he learned not only biological chemistry but also the skills to operate Mabry's NMR spectrometer. Next, Dr. Gill announced that an endowment had been created ("Professor Tom J. Mabry Endowed Excellence Fund in Phytochemistry and Plant Biology") to provide awards for research excellence by outstanding graduate students in the plant sciences.

In a letter to me, Dr. Bonness, who finished in 1992, described Dr. Mabry as "undeniably the BEST major professor that anyone could have wanted, always supporting his students above and beyond the call of duty". She recalled how he championed his students for awards, TA positions, fellowships and so many other opportunities. And when he couldn't provide advice himself he arranged meetings with key people in that particular area of research, which often led to successful collaborations. Now, almost twenty years later, my personal experience as Dr. Mabry's last graduate student echoes Dr. Bonness's feelings in every way. Of course, the lab is a much different place now since it is nearing closure, but I still feel lucky to be able to enjoy everyday his untamed enthusiasm for science, for teaching and for life in general (Figure 12).

From the many individuals who have known and had the pleasure of working closely with Dr. Mabry, including myself, we would like to express our deep appreciation and affection for him, especially on the occasion of his 75th birthday. There is no question that his career-long dedication to outstanding research and teaching excellence has impacted the field of phytochemistry and inspired many lives forever.

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