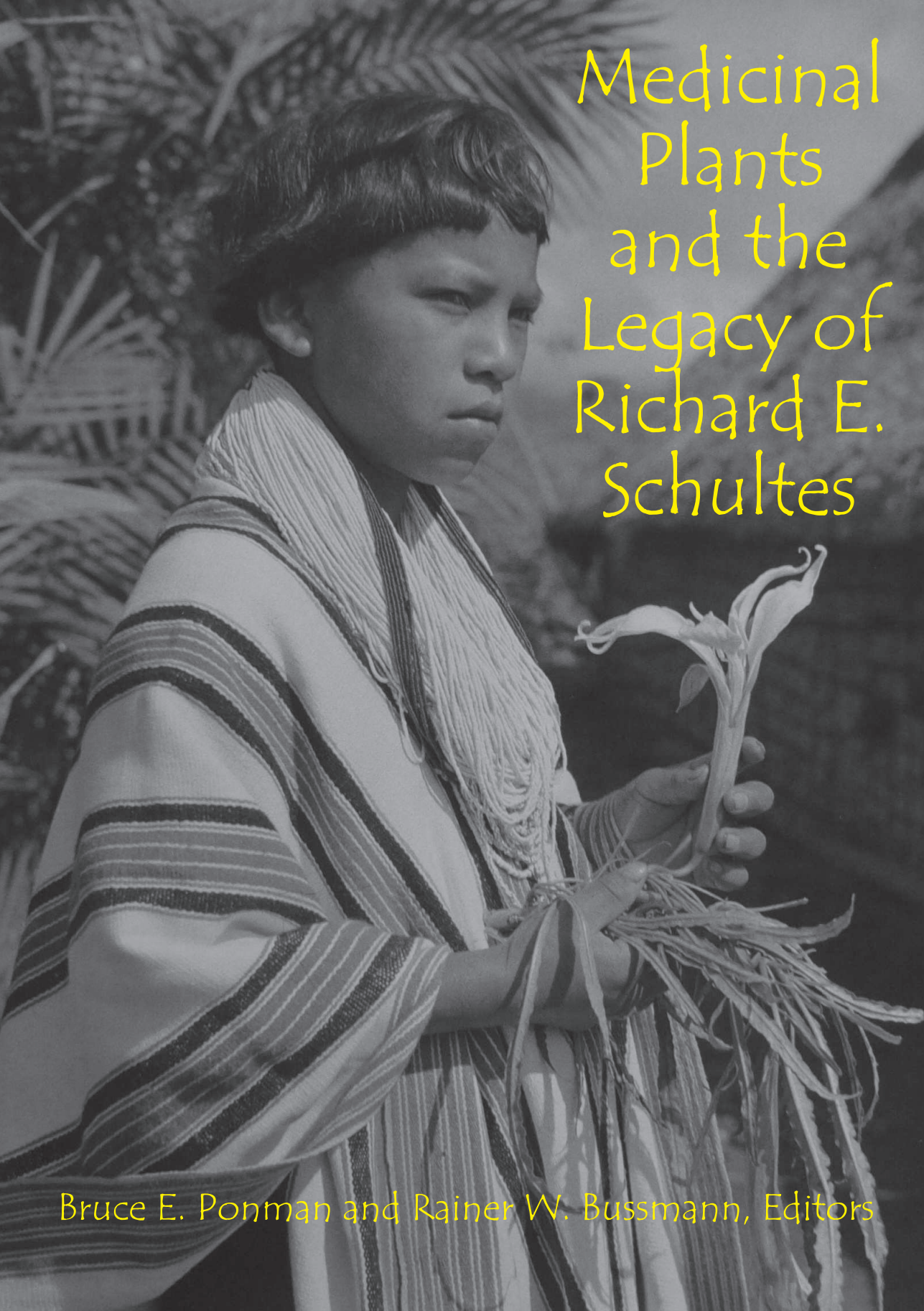

Medicinal Plants and the Legacy of Richard E. Schultes

Bruce E. Ponman and Rainer W. Bussmann, Editors

Impreso en GRAFICART SRL
San Martín 375 - Trujillo, Perú

ISBN-10: 0984841520
ISBN-13: 978-0-9848415-2-3

Hecho el Depósito Legal en la Biblioteca Nacional del Perú N° 2012-07285
Primera edición, Trujillo, Perú, mayo del 2012

Impreso en Perú
Printed in the Peru

Front cover photo by Richard E. Schultes.
Back cover image: Painting of R.E. Schultes in the Nash Laboratory, by Hannah Barrett. Courtesy of Harvard University Herbaria.

The Healing Forests of Richard Evans Schultes: Inspiration for Conservation and the Search for New Drugs Derived from Ethnobotanical Research on Tropical Forest Plants Used in Traditional Medicine.

Steven R. King[1]

The legacy of Richard Evans Schultes has so many facets it is difficult to do justice to the myriad of people, organizations, forests, and countries that he impacted. He had a profound influence on my life and the development of the soon to be approved new pharmaceutical drug *crofelemer* for the treatment of HIV/AIDS chronic diarrhea. Dr. Schultes was one of the inspirations for, and a founding scientist of, the Shaman Pharmaceuticals Scientific Strategy Team. He provided critical guidance for the work of Shaman Pharmaceuticals from 1989 until his passing in 2001. He was a vocal advocate for the approach of short, medium, and long term reciprocity conducted by Shaman with all of it collaborators. He also strongly supported the creation of the non-profit benefit sharing organization created by Shaman to return a portion of the profits of any drugs to the countries and cultures which collaborated with Shaman field research teams. The classic book, *The Healing Forest*, authored by Dr. Schultes and his friend and colleague Robert Raffauf, inspired the name for this non-profit organization, The Healing Forest Conservancy. The book documents close to 1500 species of medicinal plants utilized in the Northwest Amazon. Dr. Schultes focused on many aspects of the biocultural diversity of tropical forests and indigenous knowledge. He was also a very gifted photographer, and his photographs have been published in several books. The most notable is a wonderful book of his exquisite black and white photographs entitled *The Lost Amazon: The Photographic Journey of Richard Evans Schultes* (2004), which was produced by Wade Davis, whose chronicle of Dr. Schultes life, *One River* (1997), is mentioned in the contribution by Michael Balick in this volume.

My introduction to Richard Evans Schultes was similar to the experience of many other people. I returned to the United States after living with an indigenous community of Angotere Secoya people in the Northern Peruvian Amazon in 1979. I had lived among this community for nine months, studying their diet and medicinal plants as part of a contract with a Peruvian non-governmental organization. I visited the Field Museum of Natural History in Chicago, where I had the good fortune to meet Timothy Plowman, one of Schultes greatest students. Tim became a lifelong friend and mentor, and he also directed me to visit Dr. Schultes at the Botanical Museum on way back to college in Maine. When I visited Schultes and described where I had been conducting fieldwork, he immediately stated that I had been working in "his country with his people," as the Secoya are closely related to several cultural groups that he worked with in adjacent regions of Colombia. Dr. Schultes also became for me, as did for so many young scientists, a lifelong mentor and continuing source of inspiration.

I tried to become a graduate student of Dr. Schultes, but by the time I received my degree in Human Ecology, he was working part time and was no longer accepting graduate students. He suggested I pursue my graduate studies with one of his students, Micheal Balick, and another colleague of his, Ian Prance. I took his advice and continued my ethnobotanical

[1] Senior Vice President Sustainable Supply, Ethnobotanical Research and IP, Napo Pharmacetucials Inc. 185 Berry Street, San Francisco, CA 94107. Email: sking@napopharma.com.

Figure 1. Richard Evans Schultes conducting Dragendorff spot alkaloid field test in Colombian Amazon. Photo courtesy of R.E. Schultes.

studies in South America as part of the newly formed Institute of Economic Botany of the New York Botanical Garden.

After earning my degree in Biology, I worked for the National Academy of Sciences and then the Nature Conservancy. In 1989, Lisa A Conte, the founder of Shaman Pharmaceuticals, visited Dr. Schultes in Cambridge, Massachusetts, to learn about the feasibility of creating a pharmaceutical company that focused on ethnobotany as a source for discovering and developing new drugs. Dr. Schultes was highly supportive and shared with Lisa his enthusiasm for this project. He offered to be part of the Scientific Advisory Board of the company and directed her to many other ethnobotanists, ethnopharmacologists, and chemists, who shared his passion for the search for new drugs based on traditional ethnobotanical knowledge. He also indicated that such a company would need to have a full time ethnobotanist on the staff, not simply a person working on the outside as a consultant. Lisa visited Schultes several times and stayed in close contact with him as she sought to fund and create the company. Dr. Schultes also suggested Michael Balick as another key ethnobotanist to help her structure the company. Mike Balick also indicated it would be critical to have an ethnobotanist on the staff. I was identified by both Schultes and Balick as a good match for this work, and I was hired shortly after the first round of funding was obtained by Lisa Conte. Several of the first Scientific Strategy Team (SST) meetings took place in Cambridge, in order to be near Drs. Schultes and Raffauf, who were core scientists

guiding the medicinal plant collection and analysis of these plants.

During one of the early SST meetings, a series of plants were identified as high priority research candidates, and one of those plants was *Croton lechleri* or Sangre de Drago. The red latex of this species was and is used widely in the Northwestern Amazon Basin to treat a number of conditions, including a topical application to heal wounds and orally to treat coughs, flu, ulcers and gastrointestinal disorders, including diarrhea (Ubillas et al. 1994). The company began focusing on the screening and development on this plant and several others from Africa and South East Asia.

In 1990, as these activities were getting underway, Dr. Schultes and Robert Raffauf published the book *The Healing Forest: Medicinal and Toxic Plants of the Northwest Amazon* (Schultes and Raffauf 1990). Dr. Raffauf was a friend and professor of pharmacognosy and medicinal chemistry at the College of Pharmacy and Allied Health Professionals at Northeastern University. Raffauf had spent 25 years in the pharmaceutical industry and had participated in several expeditions in the Amazon with Dr. Schultes and his students. The book contains information about 1500 species of plants used in traditional medicine from Brazil, Colombia, Ecuador, and Peru. These represented 596 genera and 145 plant families. At the time of the writing of the book, approximately 50% of the species mentioned had not been investigated for their chemical or pharmacological properties. *The Healing Forest* represented the fruits of close to 50 years of ethnobotanical fieldwork by Dr. Schultes. This was of course only a portion of the scientific focus of Dr. Schultes, and his other areas of research expertise have been described extensively in this volume and other publications.

Figure 2. Richard Evans Schultes interviewing Salvador Chindoy a key Kasma informant and colleague in the Sibundoy of Colombia. Photo courtesy of R.E. Schultes.

Dr. Schultes had been, for decades, urging the world to research, document, conserve, and respect the indigenous peoples and their knowledge of the tropical forests, long before it became a cause célèbre for international environmental organizations, human rights groups, and the concerned public. In the forward to the book *The Healing Forest*, Prince Philips noted:

> The plants and people of the Amazon alike are under severe pressure. Schultes and Raffauf emphasize the importance of ethno-

> botanical conservation, and call attention to the fact that from these plants might come new chemical compounds of value to modern medicine and industry. It is their hope that the book will not only alert future generations of phytochemists to the potential of the Amazon as a source of new medicinal, toxic or other useful compounds, but in doing so will assist in the conservation of the folklore record of the indigenous peoples concerning this richly endowed region which is so critically important to the welfare of mankind.

Indeed Dr. Schultes devoted numerous publications to document ethnobotanical and ethnomedical knowledge. This included his own analysis of the records of early explorers of the Amazon for notes and clues indigenous ethnobotanical knowledge. A few of the titles to his article below provide glimpse of his passion for this topic.

- Ruiz as an Ethnopharmcologist in Peru and Chile (Schultes 1980)
- Several Unpublished Ethnobotanical Notes of Richard Spruce (Schultes 1985)
- Psychoactive Plants in Need of Chemical and Pharmacological Study (Schultes 1984)
- Burning the Library of Amazonia (Schultes 1994)
- Ethnnopharmacological Notes on the Flora of Northwestern South America (Schultes 1980)
- Notes, Primairly of Field Tests and Native Nomenclature, on Biodynamic Plants of the Northwest Amazon (Schultes 1983)

Research and development work at Shaman Pharmaceuticals continued throughout the entire decade of the 1990s on multiple plant extracts collected by teams of ethnobotanist and western trained medical doctors, who learned from indigenous men and women about plants used to treat infectious diseases, diabetes, and central nervous system disorders. The compound isolated from *Croton lechleri* SP-303, now known as crofelemer, continued through multiple phases of FDA-monitored clinical trials in the United States, Mexico, Venezuela, and Jamaica (Holodniy et al, 1999, DiCesare, et al 2002). The clinical indication for crofelemer became focused on diarrheal diseases, based in part on the ethnomedical usage of *Croton lechleri*.

The compound crofelemer as it turned out, was essentially not absorbed and this also made it an ideal compound to treat diarrheal diseases in the gut without having interactions with other drugs that may be absorbed. Research on the mechanism of action on crofelemer indicates that the compound appears to simultaneously target two distinct chloride channels. These channels, the cystic fibrosis transmembrane conductance channel regulator (CFTR) and the calcium activated chloride channel (CaCC) are located on the luminal membrane of the epithelial cells lining the intestines (Gabriel et al. 1999, Tradtranip et al. 2009). Crofelemer inhibits chloride secretion and reduces the gastrointestinal fluid accumulation and helps stop dehydration from excessive fluid loss.

In the time period from 2001, the year of Dr. Schultes' death, to the present in 2011, additional human clinical trials were conducted in the United States, India, and Bangladesh. Multiple studies demonstrated efficacy for the treatment of several diarrheal diseases, including infectious diarrhea and cholera-induced diarrhea (Crutchely et al. 2010). In November of 2010, the data for the final

Figure 3. Richard Evans Schultes examining his photographs at special exhibition at Stanford University in November 1992 with Lisa A. Conte. Photo courtesy of Shaman Pharmaceuticals Inc.

Phase 3 pivotal clinical trial, called ADVENT, were announced. Crofelemer demonstrated highly statistically significant results in the treatment of chronic diarrhea in people living with HIV/AIDS. The p-value achieved in this double-blind, placebo-controlled, two-stage, adaptive-design phase 3 study was 0.0096. Crofelemer was well tolerated, and the adverse event profile was not different from the placebo controlled group.

This positive Phase 3 data on a drug derived from ethnobotanical research on plants utilized by indigenous people of the Northwest Amazon will now lead to the filing of a New Drug Application (NDA) with the U.S. FDA in 2011 or 2012. In addition, a pediatric formulation of crofelemer is being developed, so that this non-absorbed anti-secretory first-in-class new chemical entity can be provided to children and communities where diarrheal disease still kill more then 1.5 million children per year. Crofelemer will become, along with oral rehydration solutions (ORS), zinc, cleaner water supplies, and increased sanitation, part of the global public health solution to stopping the huge rate loss of children's lives around the world. One of the primary goals of the founder of Shaman Pharmaceuticals Inc., Lisa Conte, this author, and the majority of the original Scientific Strategy Team (SST) members, including Dr. Schultes, was to be sure there would be and is global access to this novel, safe anti-diarrheal drug. This focus on global access will be accomplished by ex-

Figure 4. Portrait of Richard Evans Schultes at the opening of his Stanford University photographic exhibit, November 1992. Photo Courtesy of Shaman Pharmaceuticals Inc.

perts now working on a global access strategy for crofelemer, including Lady Neelam Sekhri Feachem of Napo Pharmaceuticals Inc.

One of the other core concerns of Dr. Schultes was the survival of both the tropical forest peoples and the tropical forest ecosystems. There is little disagreement that the peoples and communities who live in tropical forests share the similar aspirations for their families as the rest of the world. Those aspirations include access to health care, food, education, shelter, and the ability to provide a safe and secure long-term environment for their families. Due to the complex chemical structure of crofelemer, it cannot be made commercially via a synthetic process. The latex of this species is required for the isolation and purification of crofelemer. The latex of the *Croton lechleri* tree is sustainably harvested by local and indigenous communities and manufactured from this latex in collaboration with Napo Pharmaceuticals and its international partners. The sustainable harvesting process provides local people and communities with income generating activities, while they continue to live in and around primary and secondary forests.

The purpose of this brief paper is to pay proper homage and respect to one of the many visions, goals, passions, and accomplishments of Dr. Schultes. He was well aware of the drugs that had already been developed for the world pharmacopeia from plants used as medicines and poisons by the indigenous

people of the New World. Dr. Schultes was tremendously supportive of Shaman Pharmaceuticals. He attended all of the Scientific Strategy Team meetings, provided numerous suggestions on plants we should study, and directed young and elder scientists to correspond with Shaman Pharmaceuticals on a regular basis. He also was quite outspoken if he had concerns about the scientific direction of the company and at times he expressed concern that the core ethnobotanical knowledge, which was the unique advantage of the ethnobotanical drug discovery process, was not being fully or adequately applied in the day-to-day operations. We always listened very carefully to his guidance, followed up on any and all plants leads that he suggested, and solicited his opinion on many aspects of the overall direction of the company. He wrote many very thoughtful and kind notes to me after our SST meetings, and expressed his empathy and compassion to Lisa Conte and me on several occasions. He was pleased when the non-profit organization created to return benefits from drugs developed was named The Healing Forest Conservancy. He was even more pleased when Ms. Katy Moran, a highly respected anthropologist, became the executive director of The Healing Forest Conservancy.

The development of this drug, crofelemer, soon to be finally approved by the FDA, is part of the legacy of Richard Evans Schultes. His wonderful personal manner of supporting so many people was extended to us all. A large percentage of the members of SST have been his students, directly or indirectly. These scientists, such as Michael Balick, shared Dr. Schultes' humility, sense of humor, respect for indigenous peoples, love for Amazonia and Colombia, in particular. All of us who had the good fortune and honor to work with Dr. Schultes are deeply grateful to him for his inspiration, discipline, and vision. He has been and continues to be in my heart each day.

Acknowledgment

I would like to also pay homage to the indigenous people and communities that have collaborated with us on the discovery and development of crofelemer. I would also like to be sure to acknowledge Lisa Conte and the literally dozens of scientists who have contributed to the SST and the operations of the companies Shaman Pharmaceuticals and Napo Pharmaceuticals over the past 20 years. They also are due great thanks and appreciation for their work on crofelemer and the many other plants that have been and are part of the ethnobotanical drug discovery process.

Literature Cited

Crutchley, R., J. Miller, and K. Garey. 2010. Crofelemer, a novel agent for treatment of secretory diarrhea. *Annals of Pharmacotherapy* 44.

Davis, W. 1997. *One River: Explorations and Discoveries in the Amazon Rain Forest*. Simon & Schuster, New York.

———. 2004. *The Lost Amazon: The Photographic Journey of Richard Evans Schultes*. Chronicle Books, San Francisco.

DiCesare, D., H.L. DuPont, J.J. Mathewson, et al. 2002. A double blind, randomized, placebo-controlled study of SP-303 (Provir) in the symptomatic treatment of acute diarrhea among travelers to Jamaica and Mexico. *Am J Gastroenterol* 97:2585–2588.

Gabriel, S.E., S.E. Davenport, R.J. Steagall, V. Vimal, T. Carlson, and E.J. Rozhon. 1999. A novel plant-derived inhibitor of cAMP-mediated fluid and chloride secretion. *Am J Physiol* 276:G58–G63.

Schultes, R.E. 1980. Ruiz as an Ethnopharmcologist in Peru and Chile. *Botanical Museum Leaflets* 28(1):87–122.

———. 1980. Ethnnopharmacological Notes on the Flora of Northwestern South America. *Botanical Museum Leaflets* 28(1).

———. 1983. Notes, Primarily of Field Tests and Native Nomenclature on Biodynamic Plants of the Northwest Amazon. *Botanical Museum Leaflets* 29(3):251–272.

———. 1984. Psychoactive Plants in Need of Chemical and Pharmacological Study. *Proc Indian Acad Sci (Plant Sci)* 93(3):281–304.

———. 1985. Several Unpublished Ethnobotanical Notes of Richard Spruce. *RHODORA* 87(851):439–441.

———. 1994. Burning the Library of Amazonia. *The Sciences* March/April:24–30.

Schultes, R.E., and R.F. Raffauf. 1990. *The Healing Forest: Medicinal and Toxic Plants of the Northwest Amazon*. Dioscorides Press, Portland, Oregon.

Tradtrantip, L., W. Namkung, and A.S. Verkman. 2010. Crofelemer, an Antisecretory Antidiarrheal Proanthocyanidin Oligomer Extracted from *Croton lechleri*, Targets Two Distinct Intestinal Chloride Channels. *Molecular Pharmacol* 77:69–78.

Ubillas, R., S.D. Jolad, R.C. Bruening, M.R. Kernan, S.R. King, D.F. Sesin, M. Barrett, C.A. Stoddart, T. Flaster, J. Kuo, F. Ayala, D. Smee, R. Sidwell, K. Soike, A. Brazier, S. Safrin, R. Orlando, P.T. Kenny, N. Berova, and K. Nakanishi. 1994. SP-303, an antiviral oligomeric proanthocyanidin from the latex of *Croton lechleri* (sangre de drago). *Phytomedicine* 1:77–106.

Medicinal Plants and the Legacy of Richard E. Schultes was an all-day event held at the Botany 2011 meetings in St. Louis in honor of Dr. Richard E. Schultes. Professor Schultes was one of the great botanical explorers of the Amazon Basin, whose work redefined the discipline of Ethnobotany. Contributors recounted his work and the research it inspired.

Contributors include:

- Michael J. Balick, New York Botanical Garden
- Rainer W. Bussmann, WLBC, Missouri Botanical Garden
- Robert Bye, Universidad Nacional Autónoma de México
- Rodrigo Cámara-Leret, Universidad Autónoma de Madrid
- Andrés Gerique, Institute of Geography, University of Erlangen-Nuremberg
- Aline Gregorio, California State University, Fullerton
- Steven R. King, Napo Pharmaceuticals
- Manuel J. Macía, Universidad Autónoma de Madrid
- Narel Y. Paniagua Zambrana, Universidad Autónoma de Madrid
- Leaa Short, California State University, Fullerton
- Neil P. Schultes, The Connecticut Agricultural Experiment Station
- Djaja D. Soejarto, University of Illinois at Chicago
- Robert Voeks, California State University, Fullerton
- James S. Zarucchi, Missouri Botanical Garden

WLBC
The William L. Brown Center

Missouri Botanical Garden

$24.95
ISBN 978-0-9848415-2-3
52495>
9 780984 841523