Fifth Annual

Alice Louise Reynolds Lecture

Presented by

Paul Alan Cox
Professor of Botany
Brigham Young University

April 8, 1993

Friends of the Brigham Young University Library

Provo, Utah

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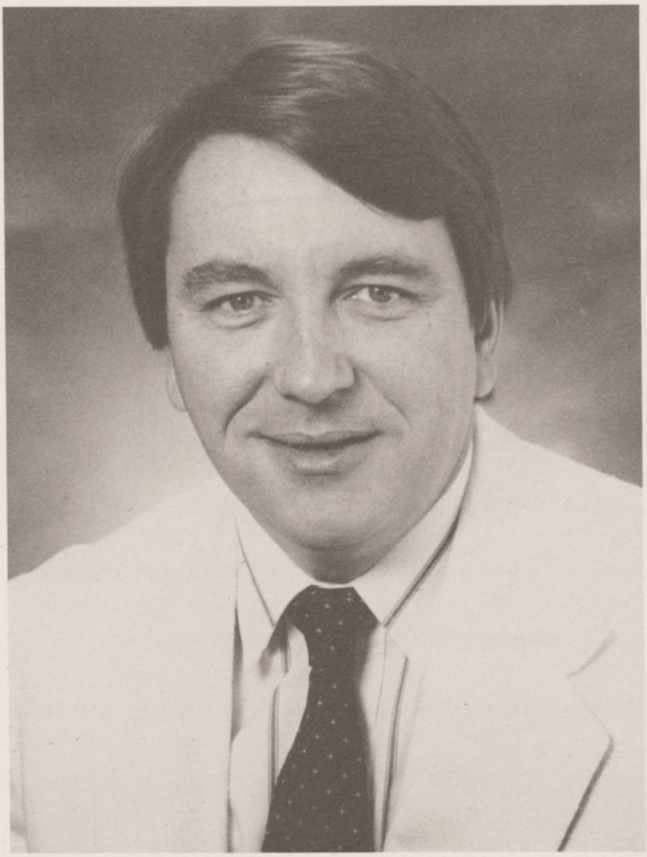
PAUL ALAN COX

A native of Utah, Professor Paul Alan Cox acquired his love of science from his late mother, fisheries biologist Rae Gabbitas Cox, and his love of conservation from his father, park ranger Leo A. Cox. Following graduation from Orem High School in 1971, he received a Joseph Fielding Smith Scholarship to Brigham Young University. An LDS mission call took him to Samoa in 1973 and 1974, where he developed his interest in tropical rainforest biology and ethnobotany. In 1975 Professor Cox married Barbara Ann Wilson, a BYU mathematics graduate. In 1976 he graduated *summa cum laude* with highest honors in botany and philosophy. A Fulbright Fellowship took him to the University of Wales for a master's degree with a pioneer of plant population biology, John L. Harper. He entered Harvard as a Danforth Fellow and as a National Science Foundation Fellow. He was awarded in 1978 and again in 1981 Harvard's most prestigious prize, the Bowdoin Prize in English Literature, becoming one of the first individuals since Ralph Waldo Emerson to receive the Bowdoin Prize twice. Professor Cox received his Ph.D. in biology from Harvard University in 1981.



Paul Alan Cox

He was then appointed a Miller Fellow at the Miller Institute for Basic Research in Science at the University of California, Berkeley, a position he held until he joined the BYU faculty in 1983. In 1985 he was awarded a National Science Foundation Presidential Young Investigator Award by President Reagan. He has held visiting appointments at Melbourne University and at Uppsala University and Umea University in Sweden. In 1991 he was invited to address the Royal Society of London.

Professor Cox has published 70 scientific articles and his first book, *Islands, Plants, and Polynesians*, appeared last year. He has gained international recognition for his struggle to preserve the rainforests and cultures of the South Pacific.

He helped spearhead a successful effort to establish a National Park in American Samoa in 1988. The following year, Professor Cox helped to raise funds to save the 30,000 acre Falealupo rainforest in Western Samoa from logging, creating one of the world's first indigeneously controlled rainforest reserves. For this achievement, the Samoan people conferred upon him one of the highest chief titles of Samoa, *Nafanua*. He was also honored by King Gustav and Queen Sylvia of Sweden, who invited him to present a command lecture in Stockholm.

Professor Cox was also instrumental in the creation of three new rainforest preserves, totalling 65,000 acres of lowland rainforest. As a delegate to the Convention of International Trade in Endangered Species in Switzerland he helped gain international protection for endangered Pacific flying foxes. He is cofounder of the nonprofit foundation Seacology, which seeks to preserve rainforests and cultures throughout the South Pacific.

Professor Cox is coauthor of "American's Academic Future," an influential report on undergraduate teaching published by the National Science Foundation. He was honored in 1988, 1991, 1992, and 1993 as "Teacher of the Year" in the Botany and Range Science Department and was chosen "Professor of the Year" at BYU in 1988. Professor Cox is Chairman of the Board of the Meridian School, a private college preparatory school in Provo. His greatest enjoyment comes from his four children: Emily, Paul Matthew, Mary, and Hillary.

The Alice Louise Reynolds Lecture

The Paradise of Plants: Realizing the Promise of 16th-Century Botany for 21st-Century Medicine

Brigham Young University, April 8, 1993

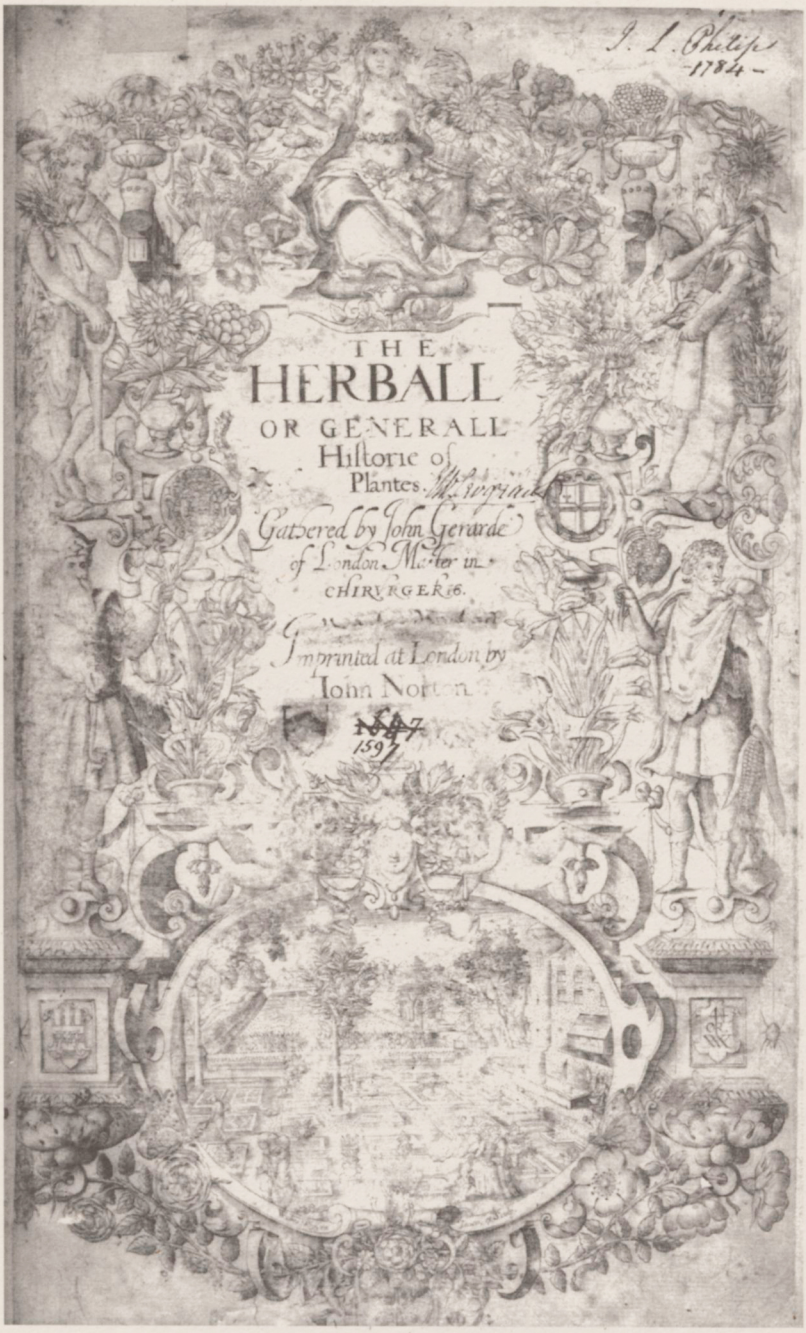
I am delighted to have this opportunity to deliver the fifth annual Alice Louise Reynolds lecture. Since the previous Reynolds lecturers have all been senior scholars with distinguished records in the humanities, I am somewhat surprised that this honor was bestowed on a young scientist. Yet as I consider the devotion of Alice Louise Reynolds to increasing the collections of the University library, it is clear all disciplines, including the sciences, have been blessed by her diligence. Perhaps too often, the efforts of Alice B. Reynolds and her successors in carefully building the collections of the library have gone unnoticed.

Perhaps too often the older books, and particularly those housed in the rare books vault, are regarded as being little more than museum pieces, with only peripheral relevance to modern thought and scholarship. If I accomplish nothing else in this lecture, I hope to dissuade you of this notion. To touch and hold an old book is

to me a nearly religious experience. The smell of the leather binding, the marginal notes scribbled in the pages, the heft and weight of an old book force me to confront the immediacy of the lives of the people who wrote and produced it in a way that no CD ROM or microfiche copy ever could. And this experience, at once both sensual and spiritual, every so often allows me to enter into a intellectual dialogue of sorts with those long since dead.

Today I wish to tell you the tale of two such books: one published nearly 400 years ago and another prepared over 200 years ago, but never published. I hope to convince you that our discussion of these two old works is not merely academic: probably a few of you in this audience are alive today because of a plant described in the 400-year-old book. And one or two of you may have sick friends or loved ones that might be blessed by a nondescript tree described in the unpublished 200-year-old volume.

I hold in my hand the 1st edition of *The Herball, or General Natural History of Plants*, by John Gerard, published in 1597. Obviously Gerard's *Herball* was not the first book published dealing with plants. Theophrastus, Hippocrates, and most importantly, Dioscorides codified and disseminated much earlier knowledge concerning plant medicine. As can be seen in Dioscorides, two pieces of



John Gerard's *The Herball, or General Natural History of Plants,* 1597

information were disseminated concerning each plant: its purported healing properties and its identification. The necessity of precise identification led to an unusual feature of early botanical iconography: for nearly two thousand years plants in herbals were pictured with the part most likely to be in medical commerce: their roots.

In the English-speaking world, the first herbal is an 11th-century Anglo-Saxon codex known as the Herbarium of Apuleius Patonicus. The earliest printed English herbal is an anonymous quarto from 1525, imprinted by Richard Banckes:

> Her beynneth a newe matter, the whiche sheweth and treateth of y vertues and proprytes of herbes, the whiche is called a Herball.[1]

A year later a translation of a French herbal was published by Peter Treversi, and in 1538 William Turner published *Lebellus de re Herbaria Nova*. In 1551, Henry F. Lyte, author of "Abide with Me," published a translation of Dodoen's famous herbal. And in 1555, Anthony Askham published a herbal derived from the 1525 English work of Banckes. But the most popular of all 16th-century herbals was that of John Gerard, published in 1597.[2]

Gerard was born in Nantwich, Cheshire, in 1545. At the age of 16, he began a seven-year apprenticeship to a London barber and

Portrait of John Gerard from his 1597 *Herball*

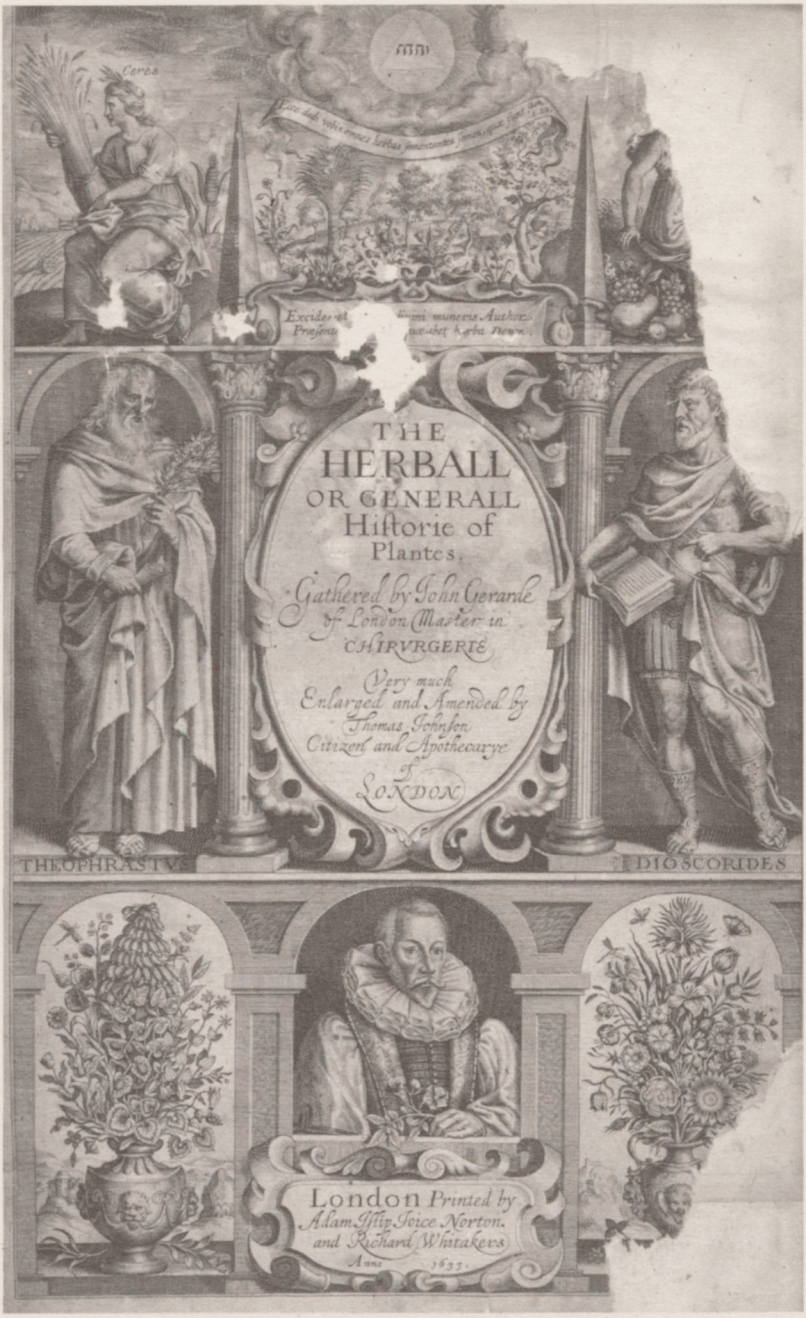
surgeon, Alexander Mason.[3] Gerard travelled briefly as ship's surgeon in the Baltic but showed far more interest in plants than in life at sea. In 1577 Gerard was appointed as superintendent of the gardens of Lord Burleigh at the Strand in London and later was appointed curator of the Physic Garden of the College of Physicians of London. Gerard established his own gardens as well, at Holborn, London, which became a veritable paradise of plants. George Baker, surgeon to Queen Elizabeth, visited Gerard's garden and found it populated with

> all manners of strange trees, herbes, rootes, plants, flowers, and other such rare things, that it would make a man woonder, how one of his degree, not having the purse of a number, could ever accomplish the same. I protest upon my conscience, I do not think for the knowledge of plants that he is inferior to any.[4]

In 1596, Gerard published a catalog of plants in his garden. But the work he published the next year, *The Herball, or General Natural History of Plants*, rapidly became one of the most quoted botanical works ever published. Gerard's *Herball*, with 1,392 pages and 2,200 woodcut images of medicinal plants, was greeted with tremendous enthusiasm by medical practitioners and the general public. The copy which I hold in front of you was conveyed from generation to generation, passing from the hands of surgeons, to

apothecaries, and even to one minister, whose estate sold it at a rare book auction in 1784—one year after the American Revolutionary War. Many of its former owners lovingly wrote detailed notes in the margins. Gerard's *Herball* has been reprinted several times and today is currently in print in a Dover edition, a remarkable feat for a book nearly 400 years old.

I find Gerard's *Herball* both informative and charming, for Gerard lived in the age when the nether regions of the world were still being explored. His struggle in determining whether the banana (which he termed the Adam's Apple tree) was a tree or a herb, is somewhat amusing (''Whether this plant may be reckoned for a tree properly, or for a herbie tree, it is disputable''), as was his obvious displeasure with the fruit (''the fruit hereof yeeldeth but little nourishment'').[5] His description of the medicinal properties of *Filipendula* (which we now call *Spirea*, a genus in the rose family) led to the isolation of salicin and the eventual synthesis of ''*A Spirea n*'' or aspirin. Quite obviously my delight in the book was shared by previous generations. And yet as we examine this copy, we see on the title page an interesting alteration: in the 18th century someone attempted to alter the date of publication from the first edition date of 1597 to the second edition date of 1633. The attempt is clumsy



John Gerard's 1633 *Herball*

and painfully obvious, since the title pages of the two editions are completely different. But this raises an interesting question—why would one try to palm off the first edition of such a valuable book as the second edition? Such action reminds me of the unschooled athlete at the last Olympics who was so thrilled with winning the gold medal that he took it to have it bronzed.

The answer lies in a bit of bibliographic intrigue. Even though Gerard's *Herball* was immensely popular, the first edition had some flaws that were corrected by Thomas Johnson in the enlarged and revised edition of 1633.[6] Some of these were nomenclatural squabbles, but there were more serious errors involving the labeling of the woodcut illustrations. Since herbals were used to compound prescriptions, such a plant misidentification could have had very serious consequences. One can only think what would have happened to Gerard had 16th-century England been as enamored with medical malpractice litigation as 20th-century America is! But fortunately many of these errors were corrected by De l'Obel prior to the first edition of Gerard's herbal going to press.[7]

Yet one of the alleged flaws was so serious that even recent scholars have deemed it unforgivable. In a very distinguished history of herbals, Agnes Arber wrote:

> The value of Gerard's work must inevitably be at a discount, when we realize that it is impossible, from internal evidence, to accept him as a credible witness. His oft quoted account of the "Goose-tree", "Barnakle tree" . . . removes what little respect one may have felt for him as a scientist . . . not because he held an absurd belief, which was widely current at the time, but because he described it, with utter disregard for truth, as confirmed by his own observations.[8]

The venerable Charles Raven, Master of Christ's College at Cambridge, wrote of Gerard that

> it is difficult to treat as a serious witness one who could so solemnly state what was in fact false; and the value of his records must be written down accordingly.[9]

The source of this controversy is Gerard's description of the "Goose Tree, Barnakle tree, or the Tree Bearing Geese":

> What our eyes have seen and hands have touched, we shall declare. There is a small island in Lancashire called the Pile of Foulders, wherein are found the . . . trunks or bodies with the branches of old and rotten trees, cast up there likewise: whereon is found a certaine spume or froth, that in time breedeth unto certain shels, in shape like those of the muskle, but sharper pointed, and of a whitish colour; wherein is conteined a thing in forme like a lace of silke finely woven, as it were togither, of a whitish colour; one ende whereof is fastened unto the inside of the shell, even as the sish of Oisters and Muskles are; the other ende is made fast unto the belly of a rude mass or lumpe, which in time cometh to the shape and forme of a bird.[10]

Barnakle Tree from Gerard's 1597 *Herball*

Gerard also found a waterlogged tree between the coast of Dover and Rumney, which when brought ashore had "many thousands of long crimson bladders" at the end of which grew small shells:

> I found within them living things without forme or shape; in other which were nearer come to ripeness, I found living things that were very naked, in shape like a Birde; in others the Birds covered with soft downe, the shell halfe open, and the Birde readie to fall out, which were no doubt the foules called Barnakles.[11]

Gerard's account of a tree producing birds stretched even my rather liberal understanding of the inherent plasticity of plant reproduction. But, unwilling to let sleeping dogs lie (or should I say, tree-borne geese fly), I wondered if possibly Gerard had not lied, but had merely misinterpreted what he had seen. I asked an expert on barnacles, BYU professor Lee Braithwaite, to see if there is anything within a barnacle that might just appear to an untrained eye as being birdlike.

Professor Braithwaite informed me that a species of the barnacle genus *Lepas*, found along the British coast on shipwrecks and dead trees, resembles Gerard's description, since it has a featherlike appendage for filter feeding.[12] I also learned that acorn barnacles have an arrangement of inner plates that protrude from their shells and resemble miniature bird beaks. We ended our discussion with an

agreement to coauthor a note on this curious matter with an eye to reinstating the integrity and good name of John Gerard.

John Gerard has also been accused of plagiarism, since much of his *Herbal* appears to be based on an earlier work, *Stirpium Historice Perptades Sex* by Dodoens (1517–1585). I find this last charge against Gerard about as disingenuous as accusing an Elvis impersonator of being derivative. I mean, that's the point, isn't it? Herbals, by definition, are accumulations of experience through the ages. Thus Dodoens's work borrowed very heavily from both Pliny and Dioscorides, who in turn borrowed from the rhizotomi, generations of nameless Greek root gatherers whose business was "the gathering, preparing, and selling of roots and herbs that were of repute in medicine."[13]

It was precisely this collection of accumulated folk knowledge that made John Gerard's *Herball* of such value. Renaissance doctors carefully searched the pages of Gerard's *Herball* for plant medicines. Take for example Gerard's entry on page 646 "of Foxe gloves":

> Foxe gloue boiled in water or wine, and drunken, doth cut and consume the thicke toughness of grosse and slimie flegme and naughtie humours; it openeth also the stopping of the liver, spleene and milt and of other inward parts.[14]

Gerard's recording of foxglove opening the stopping of "other inward parts" was not systematically examined until nearly 200 years

AN

ACCOUNT

OF THE

FOXGLOVE,

AND

Some of its Medical Uſes:

WITH

PRACTICAL REMARKS ON DROPSY, AND OTHER DISEASES.

BY

WILLIAM WITHERING, M. D.
Phyſician to the General Hoſpital at Birmingham.

——— *nonumque prematur in annum.*

HORACE.

BIRMINGHAM: PRINTED BY M. SWINNEY;
FOR
G. G. J. AND J. ROBINSON, PATERNOSTER-ROW, LONDON.

M,DCC,LXXXV.

later when, in 1785, William Withering published "An Account of the Foxglove and some of its Medical Uses, &c."[15] Withering quoted Gerard's account of the "vertues" of foxglove and proposed that foxglove could be an important medicine for dropsy.

There is certainly little in Withering's upbringing to have predicted an interest in botany. Like some of our contemporary premedical students, Withering was not enamored with the necessity of learning botany. By Withering's account, his botany professor at Edinburgh, John Hope, was quite dull. In a letter home to his parents, he wrote:

> The Botanical Professor gives annually a gold medal to such of his pupils as are most industrious in that branch of science. An incitement of this kind is often productive of the greatest emulation in young minds, though, I confess, it will hardly have charm enough to banish the disagreeable ideas I have formed of the study of botany.[16]

Withering's botanical interest lay dormant until 1775 when, as a young man, he was smitten with a beautiful girl, Helen Cookes, whom he would later marry. As so often occurs with young men in love, his mind was carried to a higher plane, where, of course, he encountered and embraced botany. It appears that Miss Cookes was an aspiring artist who wished to paint flowers. Young Withering, eager to please, began collecting plants for her to sketch. During this

Foxglove from Gerard's 1597 *Herball*

romantic interlude, the magic of plants captured Withering's imagination. Although he continued his practice of medicine, he later published several texts on botany and was elected a Fellow of the Linnean Society.

This love of plants perhaps explains why Withering, a Birmingham physician, did not reject out of hand a folk story he heard of the use of foxglove to cure dropsy:

> In the year 1775, my opinion was asked concerning a family reeeipt for the cure of the dropsy. I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. . . . This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than Foxglove.[17]

Dropsy, a retention of fluids due to inadequate pumping by the heart, was clearly affected by foxglove. The connection between dropsy and poor pumping action of the heart was not properly understood in Withering's day, even though Withering clearly observed the action of foxglove on the heart:

> That it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends.[18]

Withering began prescribing foxglove for cases of dropsy, but soon encountered dosage problems:

> I soon found the Foxglove to be a very powerful diuretic; but then, and for a considerable time afterwards, I gave it in doses very much too large.[19]

Not only was determination of dosage a problem, but Withering also had a difficulty in approaching a standardization of dosage from ground leaves:

> These I had found to vary much as to dose, at different seasons of the year; but I expected, if gathered always in one condition, viz. when it was flowering late, and carefully dried, that the dose might be ascertained as exactly as that of any other medicine; nor have I been disappointed in this expectation.[20]

Withering therefore began prescribing water infusions of the leaves (made by steeping the plant in water) and later ground leaf powder. By any standard, foxglove as administered by Withering was an astonishingly successful treatment for dropsy. J. K. Aronson at Oxford has recently reanalyzed data from the cases Withering carefully recorded, finding a success rate of between 65 and 80 percent.[21]

The Latin name of the foxglove genus, *Digitalis*, was affixed to the crude drug as well as the cardiac glycosides isolated from foxglove in the early 20th century. Cardiac glycosides are steroidal compounds with sugars attached at the 3–position and are so named because of their powerful action on the heart. These drugs are useful because they increase the force of systolic contraction, allowing the

heart more time to rest between contractions.[22] More than 30 cardiac glycosides have been isolated from dried foxglove leaves, including digitoxin and digoxin, the latter compound being marketed as Lanoxin by Burroughs Wellcome.[23] Neither of these two drugs have ever been synthesized and are still extracted from dried foxglove leaves.[24] Each year over 1500 kg of pure digoxin and 200 kg of digitoxin are prescribed to thousands of heart patients.[25] In the last 20 years it has been shown that digitalis exerts its effects on the heart by inhibiting an enzyme that powers the transport of potassium and sodium across cell membranes: sodium-potassium linked, magnesium-dependent adenosine triphosphatase (Na/K–ATPase).[26]

Although the advent of new diuretics and vasodilators have added to the repertoire of heart medicines, digoxin still saves many lives each year. As Aronson reports, "There is still no alternative to digitalis for the first line treatment of fast atrial fibrillation in the majority of cases."[27] Given the widespread use of digoxin, I would hazard a guess that there are at least one or two members of our audience who are alive today because of an extraordinary sequence of events beginning with the 1597 publication of Gerard's *Herball*, a chance conversation of William Withering with "an old woman of

Shropshire,'' and the 1785 publication of Withering's account of foxglove. In academic circles, we sometimes hear the phrase ''publish or perish,'' and perhaps for two or three of you present today, this maxim is truer than might be comfortable: had not Gerard and Withering published, you very well may have perished. May we thus dispose of the view that the old books are merely museum pieces, of no possible relevance to us today?

Publish or perish. Let me turn now to a volume that was not published and nearly did perish until it was rediscovered by a worker in the British Museum less than 20 years ago. I speak of course of Bank's *Florilegium*, the botanical illustrations to Captain Cook's first voyage of discovery to the South Pacific. In 1768, Captain James Cook was dispatched to Tahiti to record the transit of Venus. The expedition was not hatched merely to satiate the idle curiosity of astronomers: it was believed that Cook's data, when compared to similar observations to be taken in Egypt, would allow, by triangulation, an extremely accurate measurement of the circumference of the earth. This in turn would greatly improve the accuracy of map making and navigation.

Cook's orders extended beyond mere astronomy and he was instructed to return to England with ''such specimens as the seeds of

trees, of fruits and grains as you may be able to collect.'' To aid in this latter charge, Sir Joseph Banks came on the scene. Banks was young, adventurous, and rich. Self-financed, he arranged to accompany Cook's voyage as naturalist, employing Carl Linnaeus's prize student, Dr. Daniel Carl Solander (1733–1782) and an extraordinary amount of equipment. To quote Chris Humphries's account:

> When he went on board of the Endeavour he came with a party of seven, a great load of personal and scientific stores and equipment; this at a cost of about 10,000 gives an idea of how he travelled when you consider that the King's contribution to the remainder of the expedition was less than half of that. He had found ''much the best salt beef I have ever tasted'' in New Crane Street, beer from a dealer near St. Giles, porter from another at Wapping New Stairs. He had barrels of salted cabbage, and sheep, fowls and pigs. Also, two greyhounds for no Englishman would, if he could help it, go anywhere without a dog.[28]

Somehow I find the image of the young British dandy arriving in Tahiti in the company of both cabbages and greyhounds most compelling. But alas, the chosen day to observe the transit of Venus was overcast and given the necessity for synchrony of the observations, the voyage, in terms of its original mission, was futile. Yet what Banks returned with eventually eclipsed the planned astronomical observations (no pun intended), for he brought the very

first collections of Tahitian plants back to England. These plants were so unlike anything that had previously been observed by Europeans that their scientific importance as specimens can only be compared to that of the moon rocks returned to earth by the *Apollo* astronauts.

During the voyage, each plant was brought to Solander, who did a thorough botanical diagnosis, and then placed in the hands of one of the greatest botanical illustrators to ever live—Sidney Parkinson. The botanists worked in extremely cramped quarters, which they shared with 84 other crew members for three years: After seeing the *Endeavour* upon its return to England, Samuel Johnson remarked that "going to sea was like going to jail with the added prospect of drowning."

The prospect of drowning, fortunately, did not threaten the crew of the *Endeavour*, but Sydney Parkinson, bitten by a mosquito off the coast of Java, died of malaria at the young age of 25. Though the artist was dead, Parkinson's portfolio of 900 drawings and water-colors was brought to London. There, the surviving expedition members encountered the sort of reception that only astronauts have enjoyed in recent years. Elected President of the Royal Society, Sir Joseph Banks commissioned 18 of the finest engravers in the

world to inscribe Parkinson's images in copper. Hiring Solander to oversee production, Banks put up £10,000 to finish the drawings and an additional £7000 to engrave them.

The resultant engravings are exquisite and represent the apogee of botanical illustration. Over a period of 13 years, a total of 743 copper plates were engraved. Yet the swirl of scientific and social activities surrounding Banks and his ultimate death resulted in the plates' never being published. Eventually the copper plates found their way to some dark and largely forgotten cabinets in the British Museum, where they sat, prey to dust and corrosion from London smog, for nearly two centuries.

In 1978 Dr. Chris Humphries of the British Museum of Natural History and graphic artist Nigel Frith conceived of a project to publish the plates using the original techniques and tools that would have been used in Bank's times. An 18th-century printing shop was constructed on the east side of London. The edition was strictly limited to 100 images of each copper plate, and tremendous care was taken to ensure complete accuracy of the colors and continuity from print to print. Ninety-nine of the 100 sets sold immediately to art museums and other institutions. But I knew that one set, purchased by James MacEwan and Associates of London, was being split up and

sold as singles at $1400 to $3000 each. I asked if they would be willing to donate a tithe of their proceeds to fund rainforest conservation in Samoa. As a result, the premier exhibition of the 88 Society Islands prints was held in the Monte L. Bean Museum, raising sufficient funds to save over 3,000 acres of lowland rainforest.

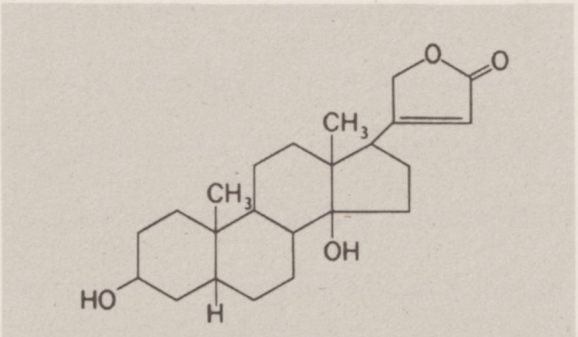
Yet some of the images did not sell, including this print #652, *Homalanthus nutans*, which was discovered by Cook's expedition in 1769. *Homalanthus nutans* is a small rainforest tree that grows throughout the islands of the South Pacific, including Samoa. This little print, though beautiful, remained with several other unpurchased prints for several years, until it suddenly assumed international importance.

Much as William Withering was told by an "old woman of Shropshire" that foxglove is useful as medicine, I was told by several "old women" during my ethnobotanical research in Samoa that *Homalanthus nutans* has medicinal properties. These "old women," known in the Samoan language as *taulasea* or healers, are heirs to a tremendous store of traditional knowledge concerning plant medicines.[29] I was struck by their suggestion that the macerated wood of *Homalanthus nutans*, a small rainforest tree of the poinsettia family (*Euphorbiaceae*), is used in water infusions to treat yellow

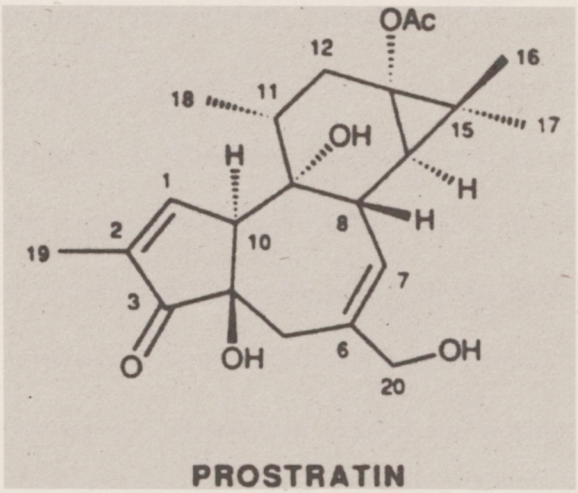
fever. This interested me, because yellow fever is a viral disease, and we have precious few compounds in our repertoire of modern medicines that are active against viruses.

The healer's method of preparation was striking. The stem wood is scraped into a clean cloth, which is tightly tied in a manner resembling a tea bag. This bag is then steeped in very hot water, producing a brown-colored infusion. The wood particles inside of the bag are discarded, and the infusion, after cooling, is drunk by the patient. I returned samples of *Homalanthus nutans* wood, together with other samples I collected, to my collaborators at the Natural Products Branch of the National Cancer Institute. There these extracts were screened by a team led by Michael Boyd for anti-HIV activity. In an *in vitro* tetrazolium-based assay to detect cytopathic effects of the AIDS virus HIV–1, *Homalanthus* extracts exhibited extremely potent activity.[30] Bioassay guided fractionation by a team led by John Cardellina and Kirk Gustafson at the National Cancer Institute resulted in the isolation of prostratin (12–deoxyphorbol 13–acetate).

Prostratin showed intense activity against HIV–1 in two different ways. First, at noncytotoxic concentrations prostratin prevented HIV–1 reproduction in lymphocytic and monocytoid cells. Secondly,



Digitoxigenin
3β,14-dihydroxy-5β,14β-card-20(22)-enolide



PROSTRATIN

prostratin also fully protected human cells from lytic effects, and hence death, from HIV–1. Yet our discovery of prostratin as the active compound was not universally regarded as good news, since prostratin belongs to a group of compounds known as phorbols. Since phorbols are known to be tumor-promoters,[31] identification of the active antiviral component of *Homalanthus nutans* as a phorbol raised serious concerns about its possible therapeutic potential. But further research revealed that in contrast to other phorbols, prostratin is not a tumor-promoter,[32] yet stimulates protein kinase C.

The National Cancer Institute has concluded that prostratin "represents a non-promoting activator of protein kinase C which strongly inhibits the killing of human host cells in vitro by HIV. By these criteria, prostratin is unique."[33]

Since *Homalanthus nutans* is a member of the phorbol-rich *Euphorbiaceae*, it is possible that it contains other phorbols that have undesirable effects. However, since prostratin is a relatively polar phorbol, and hence more easily dissolved in water, it appears that preparation techniques of the Samoan healers might serve to selectively extract prostratin from the plant. Just as modern pharmacological investigations have confirmed folk accounts of the potency of foxglove, our isolation of prostratin from *H. nutans*, its extreme potency

against HIV–1, and its unique nature as a nonpromoting protein kinase C activator tend to corroborate the Samoan use of *H. nutans* against diseases of viral origin. Currently the National Cancer Institute considers prostratin as a potential candidate for drug development.

I hasten to caution you, though, that prostratin has yet to be tested in a clinical setting, and we have no evidence that it will provide an effective therapy against AIDS in human beings. Many more careful studies, particularly of its possible toxic effects, need to be made before it can be brought to the clinic for testing. If prostratin does make it onto the market as a drug, it will probably not be before the advent of the 21st century.

Notice the similarity between the modes of discovery of digitalis and prostratin. John Gerard published a drawing and description of the foxglove in his 1597 *Herball*, yet it took nearly 200 years for William Withering to begin to investigate its possible medicinal properties. *Homalanthus nutans* was illustrated a bit over 200 years ago for the unpublished Bank's *Florilegium*, yet only within the past several years has a serious investigation been made of its possible antiviral potential. In both cases, investigators were initially spurred on by folk accounts of its use in herbal therapy.

Are there more medicines yet to be discovered in the paradise of plants with which we are surrounded? I answer a resounding "yes." Over 25 percent of the prescription drugs issued this year in the United States and Canada were originally discovered from plants.[34] These include vincristine and vinblastine, derived from the Madagascar periwinkle *Catharathus roseus* (*Apocynaceae*), which are used for pediatric leukemia; reserpine from *Raulvolfia serpentina* (*Apocynaceae*), which is used to treat hypertension; and diosgenin derived from *Dioscorea floribunda* (*Dioscoreaceae*), which is the chemical building block for many steroidal compounds, including most oral contraceptives. Although this manner of searching for new drugs may seem to be old fashioned to some, my colleagues and I in ethnobotany have been blessed with an enviable record of success in the discovery of new lead compounds. In our work we have been tremendously aided by incredible strides in the development of high-resolution bioassays that can detect pharmacological activity in crude plant samples of only a few milligrams. And natural product chemistry has rapidly developed to be able to quickly yield structural determinations of what might once have been regarded as hopelessly complex molecules.

Let me illustrate this latter point again with results from investigations of Samoan ethnopharmacology. The healers told me that

the bark of *Erythrina variegata* is useful against *fula*, a group of inflammatory diseases. Together with my colleagues at the Schering-Plough Research Institute, particularly Vinod Hegde and Mahesh Patel, I screened extracts of *Erythrina variegata* (*Leguminosae*) for inhibition of phospholipase A_2, an enzyme believed to play an important role in inflammation. Samoans recognize two varieties of *E. variegata*, "*gatae Samoa*" and "*gatae palagi*," but use the bark of only one variety, "*gatae Samoa*," to treat inflammation. We found that only the ethnovariety *gatae samoa* significantly inhibits phospholipase A_2. Using bioassay-guided fractionation, three phospholipase A_2 inhibitors were isolated and identified.[35] These include two flavonoids (4'-hydroxy-3',5'-diprenyl isoflavonone, and 3,9-dihydroxy-2,10-diprenyl pterocarp-6a-ene) and a novel isoflavonone (4'-hydroxy-3'5',6 triprenyl isoflavonone). The isolation of these anti-inflammatory compounds and the confirmation of anti-inflammatory activity in only one ethnovariety of *Erythrina variegata* lends credibility to our approach of seeking new drugs from folk medicine.

Other lead compounds have also emerged from our work. Together with my colleagues Noel Owen and David Grant in our chemistry department, and a team headed by Premila Perira and

Lars Bohlin at the University of Uppsala, we have isolated and characterized several new complex bioactive saponins from *Alphitonia zizyphoides* (*Rhamnaceae*), a tree whose aromatic bark is used in Samoan medicine.[36] In all of these discoveries, we have taken considerable measures to guarantee that any commercial development of these products will be equitably shared with the Samoan villagers. And our new nonprofit foundation, Seacology, has been instrumental in helping the Samoan people set aside over 65,000 acres of Samoan rainforest in preserves and national parks, thereby ensuring not only the survival of precious medicinal plants, but the Samoan culture as well.

The general approach pioneered by John Gerard and William Withering, namely the collection of folk knowledge concerning medicinal plants, and its systematic pharmacological investigation, remains valid today in our search for new drugs for the 21st century.[37] Careful compilation of ethnobotanical knowledge, screening of medicinal plant extracts against specific bioassays for appropriate disease targets, and bioassay-guided fractionation and isolation of pure compounds remains a very powerful approach. Subsequent tinkering by synthetic chemists and pharmacologists can possibly improve potency and mode of action of these molecules. Even if new

drugs are not discovered through this route, it is possible that new chemical building blocks or substances that reveal new modes of therapeutic action might be uncovered. Together with my collaborators at the National Cancer Institute, the University of Uppsala, Schering Research Institute, and here at BYU, we have isolated seven new lead compounds that show antiviral, anti-inflammatory, or antitumor activities. Patents are pending for two of these compounds. Of course there is only a small chance that any particular lead compound will make it through clinical trials, but if we accept generation of interesting new lead compounds as one measure of success, this approach has been very effective indeed.

My reliance on folk knowledge and older texts may cause some to criticize me for doing "old-fashioned" science. Somehow a botanist roaming the jungle with a plant press in the search of healers does not seem as "scientific" as someone in a white lab coat working in a laboratory. Yet the results of such a simple approach are now clear, and extraordinarily cost effective: for the price of one DNA sequencer I could fund the work of my students and me for more than a year. Simple, inexpensive items such as notebooks, pencils, plant presses, clippers, and machetes are the tools of my trade, but equally important are the indigenous language dictionaries,

ethnographies, and old herbals that I base my explorations on. In this regard, the efforts of Alice Louise Reynolds and her successors in building our library collections continue to bless my research.

Are the old books in the library, the books that scientists such as Gerard and Withering wrote, merely museum pieces, with little relevance to modern thought and scholarship? Absolutely not. We have scarcely begun to scratch the surface of the information contained in Gerard's *Herball*, published nearly four centuries ago. And the tremendous store of information that is held by indigenous people, "the old women of Shropshire," Samoa, Tahiti, the Amazon basin, and many other areas is only now being seriously investigated.

The time is short, as indigenous cultures are disappearing nearly as rapidly as the rainforests. Every second an area of rainforest about the size of our football stadium vanishes forever. And every week, aged healers, heirs to centuries of knowledge, pass away with their wisdom unrecorded for future generations. Yet my colleagues, students, and I are determined to continue on, for we are confident that with diligence, we can achieve the promise of 16th-century botany, the discovery of new medicines from plants, for those who will follow us in the 21st century. Thank you.

Notes

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3. I am indebted for details of Gerard's early life to C. C. Gillispie (1972), *Dictionary of Scientific Biography,* 5: 361–363, New York: Charles Scribner's Sons.
4. Ibid., preface, "George Baker, one of hir Maiesties Chiurgions in orinarie, and M. of the Chiurgions of the citie of London, to the Reader."
5. Ibid., 1331–1333.
6. Gerard's *Herball* as amended by Thomas Johnson.
7. C. E. Raven (1974), *English Naturalists from Neckam to Ray,* Cambridge: Cambridge University Press.
8. Arber.
9. Raven, 212.
10. Gerard, 1391.
11. Ibid., 1392.
12. This appendage is called a cirrus with setae and strongly resembles a bird's feather.
13. Edward Lee Greene (1983), *Landmarks in Botanical History,* edited by Frank G. Egerton, Stanford: Stanford University Press, part I, p. 121.
14. Gerard, 646.
15. William Withering (1775), *An Account of the Foxglove and Some of its Medical Uses: with Practical Remarks on Dropsy and other Diseases,* Birmingham: M. Swinney.
16. As quoted in J. K. Aronson (1985), *An Account of the Foxglove and Its Medical Uses 1785–1985,* Oxford: Oxford University Press, 251.
17. Withering, 2.
18. Ibid., 192.
19. Ibid., 2–3.
20. Ibid., 4.
21. Aronson, 273.
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27. Aronson, 351.
28. From a lecture given by C. J. Humphries of the British Museum (Natural History) at the Monte L. Bean Museum, Brigham Young University, 1990.
29. For recent accounts of Samoan herbal medicine, see P. A. Cox (1992), "Shaman as Scientist: Indigenous Knowledge Systems in Pharmacological Research and Conservations Biology," Morrison Lecture Series, Stanford University; P. A. Cox (1992), "Saving the Ethnopharmacological Heritage of Samoa," *Journal of Ethnopharmacology* 38: in press; P. A. Cox & S. A. Banack (eds.), *Islands, Plants, and Polynesians,* Portland: Discorides Press; P. A. Cox (1990), "Samoan Ethnopharmacology," 123–139, in H. Wagner & N. R. Farnsworth, *Economic and Medicinal Plant Research,* vol. 4, *Plants and Traditional Medicine,* London: Academic Press.
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