







THE JOURNAL  
OF COLLEGIUM  
AESCULAPIUM

<i>Called to Serve and to Save</i>	6
<hr/>	
ELDER RUSSELL M. NELSON	
<i>Our Medical Mission on the Other Side of Town</i>	12
<hr/>	
EDMUND C. (TED) EVANS, M.D.	
<i>A Beautiful Experience</i>	16
<hr/>	
GLORIA EVANS	
<i>COX-2 Inhibitor Drugs: The Future of Pain and Inflammation Therapy</i>	18
<hr/>	
KENNETH J. HUNT, MSII AND BRUCE H. WOOLLEY, PHARM.D.	
<i>New Treatments for Aging Skin</i>	28
<hr/>	
RICHARD W. PARKINSON, M.D.	

## About Collegium Aesculapium

In a troubled world, many LDS physicians and health care professionals have an ability to see the whole person in terms of the emotional and spiritual as well as the physical. They desire to put the teachings of the gospel into their daily lives. As they receive knowledge and gain wisdom, they can then offer understanding and give service in order to uplift and sustain the lives of their loved ones and patients.

Collegium Aesculapium addresses the spiritual as well as the physical sides of medicine. Here, thoughts transcending science challenge our exacting professions.

Join Collegium, and enhance your professional experience with insightful meetings and seminars, top LDS speakers, service opportunities, periodic newsletters, and of course, the *Journal of Collegium Aesculapium*.

For more information, see <http://www.collegiumaesculapium.org>.

## How to join Collegium Aesculapium

Collegium Aesculapium encourages physicians, podiatrists, and doctors of pharmacy to become active members of the organization (\$125 per year). Special rates are available for retired health professionals (\$75) and professionals in their first two years of practice (\$50). Nurses, physical therapists, pharmacists and others interested in the Foundation are invited to join as Associate Members (\$75 per year). Medical students in training and upper-class premedical students (\$35 per year) may also join the Collegium.

To join, send name, address, and membership fees to:

*Collegium Aesculapium Foundation, Inc.*  
P.O. Box 7424, University Station  
Provo, UT 84602-7424

## Collegium Aesculapium Board and Past Presidents

### EXECUTIVE BOARD

Marian M. Brubaker, M.D.  
Lloyd Call, M.D., *President-Elect*  
James M. Clayton, M.D.  
Homer Ellsworth, M.D.  
David G. Feil, M.D.  
Glen C. Griffin, M.D.  
Joseph P. Hardy, M.D., *Past President*  
Blayne Hirsche, M.D.  
Clayton Huber, PH. D., *Treasurer*  
Kenneth Hunt, *Med. Student Rep.*  
Karen Lewis, M.D.  
Larry Noble, M.D.  
Joseph L. Pace, M.D.  
Richard B. Sampson, M.D.  
C. DuWayne Schmidt, M.D.  
Thomas N. Spackman, M.D., *President*  
Swen Swensen, M.D.  
David S. Tensmeyer, M.D.  
George J. Van Komen, M.D.  
G. Michael Vincent, M.D.  
W. Lawrence Warner, M.D.  
Bruce Call Williams, M.D.  
Bruce H. Woolley, PHARM. D., *Exec. Vice President*

### PAST PRESIDENTS

1982 Robert H. Hales (*deceased*)  
1983 Richard A. Call II  
1984 John C. Nelson  
1985 N. Lee Smith  
1986 Robert D. Jones  
1987 Roger L. Hiatt Sr.  
1988 Joseph G. Cramer  
1989 Lattimer H. Ford (*deceased*)  
1990 Homer S. Ellsworth  
1991 Larry Noble  
1992 G. Michael Vincent  
1993 Sydney A. Horrocks (*deceased*)  
1994 Blayne Hirsche  
1995 Richard B. Sampson  
1996 Marian M. Brubaker  
1997-98 James M. Clayton  
1999 Joseph P. Hardy

THE JOURNAL OF

COLLEGIUM AESCULAPIUM

SPRING 2001

### EDITORIAL STAFF

Bruce H. Woolley, PHARM. D., Publisher  
Glen C. Griffin, M.D., Executive Editor  
Kent Staheli, M.D., MPH, Editor  
Kenneth Meyers, Managing Editor  
Kristi Brown, Associate Managing Editor

### EDITORIAL BOARD

Edmund C. "Ted" Evans, M.D., *Pediatrics*  
James O. Mason, M.D., *Public/Community Health*  
John Matsen, M.D., *Infectious Disease/Pathology*  
Guy Hartman, M.D., *Toxicology*  
Richard W. Parkinson, M.D., *Dermatology*  
A. Hamer Reiser, Jr., M.D., *Internal Medicine*  
Brent Scharman, PH.D., *Behavioral Medicine*  
Duane Schmidt, M.D., *Pulmonology*  
Charles Smart, M.D., *Internal Medicine*

Manuscripts considered for publication in the *Journal of Collegium Aesculapium* must be clinically appropriate and spiritually consistent with the principles and doctrines of The Church of Jesus Christ of Latter-day Saints. All manuscripts must be clearly written and submitted in a double-spaced 12-point, Times New Roman, Garamond, or Bookman font in a Microsoft Word or WordPerfect e-mail attachment. A manuscript that meets these standards is peer reviewed by several members of the editorial board and is evaluated with the reviews by the publisher, executive editor, and editor. After suggested content adjustments are made, an article may be accepted, edited to our standards of style and readable writing, and published in the *Journal*.

*The Journal of Collegium Aesculapium* is a peer-reviewed journal published by the Collegium Aesculapium Foundation, Inc. Articles published in the *Journal* are the sole responsibility of their respective authors, and do not necessarily reflect the opinion of the organization or any sponsoring or affiliated institutions.

© 2001 Collegium Aesculapium.  
All rights reserved.

*After years of saying “We’ll go on a mission in a couple of years,” Mary Ella and I are really going, now, to Southeast Asia!*



“When will you be ready to go on a medical advisory mission?” Quinton Harris kept asking me after my eight years as editor-in-chief of *Postgraduate Medicine*. “In a couple of years,” I answered. Mary Ella and I had looked forward to going on a mission together, but the time didn’t seem right. Besides becoming editor of this journal, I was asked to join the part-time faculties of the new UVRMC Family Practice Residency Program and of the BYU School of Family Life to create a peer-reviewed magazine, *Marriage & Families*, with an audience ranging from students to professionals.

If that were not enough, our non-profit organization created an Internet resource ([www.moviepicks.org](http://www.moviepicks.org)) to help people find wholesome movies and videos. Working with people of many faiths and cultures, including Rabbi Daniel Lapin, the late Cardinal O’Connor, and Dr. Siddiqu, the President of the North American Islamic Society, we also established CAMIE awards for *Character And Morality In Entertainment* for those who produced uplifting and decent shows ([www.CAMIE.org](http://www.CAMIE.org)).

Meanwhile, Mary Ella and I kept planning to go on a mission “in a couple of years,” or so. We felt needed by my 90-year-old parents, both of whom have coronary artery disease, and especially by my mother who had a stroke and a duodenal ulcer with massive bleeding. We didn’t know, and still don’t, how long they will be around. Besides, there were our six grown children (who never seemed to run out of problems) and our 14 grandchildren.

In a little diversion we flew to Florida in August and bought a beautiful motor-home van. We thought the unsteadiness was from the crosswinds and the 18-wheeler citrus trucks zooming by. But it was a steering mechanism defect that sent the van careening across traffic, forcing one car off the road with us into a muddy meridian — and missing a water drain and other vehicles by inches. It was a miracle no one was killed, or even hurt. This wake-up call made us realize we had more important things to do than touring the country in a luxury RV. It went back to the dealer and we flew home.

A couple months later our bishop asked us if we were ready to go on a mission. Disengaging from all we were doing would be no easy task, but we said yes. Now, we are on the way to Singapore, where Mary Ella and I will teach the gospel and try to keep our missionaries healthy — and when things go wrong to be sure they get the best medical care — in three Southeast Asia missions: Singapore (including Pakistan, Sri Lanka, and Malaysia), India Bangalore (all of India), and Indonesia Jakarta. This will be one of the most exciting challenges of our lives. It will be hard to say goodbye to our aging parents, kids, and

grandchildren, and to leave our comfortable home. But when we thought about Joseph and Brigham calling missionaries to leave sick, struggling, impoverished families to go far away and teach the gospel, we knew we couldn’t keep saying “in a couple of years.” If we waited until everyone in our family was healthy, wealthy, and problem-free, we’d never go.

Be sure to read, “Called to Serve and to Save” by Elder Russell M. Nelson, who I watched perform bypass surgery on my father and my mother when they returned from presiding in the Spain Barcelona mission. After saving their lives, and countless others in the operating room, millions more have had their lives touched by this great teacher and special witness of the Lord Jesus Christ.

Then there are inspiring articles by Ted and Gloria Evans who share their mission experiences across town on Temple Square. As you read this article, and remember John and Carolyn Bennett’s stories about serving in Mongolia, think and plan for your medical advisory mission — not if, but when.

And to get up to speed on controlling mild to moderate pain and inflammation, you’ll want to read Kenneth Hunt & Bruce Woolley’s article about COX-2 inhibitors. There’s also an article by Rick Parkinson about new treatments for aging skin — especially applicable about those who didn’t follow his advice about avoiding too much sun.

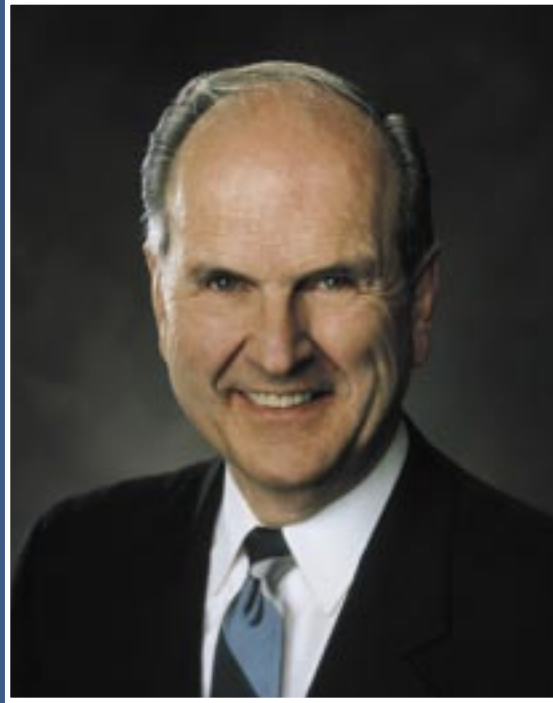
By the way, Collegium is still one of the best-kept secrets around. Every physician, podiatrist, and pharmacist in the Church should be a member. We need them — and they need the journal, outstanding meetings, spiritual insights, and association with each other.

We welcome our new editorial board members, as well as Kent Staheli, M.D., as Editor, who along with Bruce Woolley and our staff will take care of the day-to-day operation of the *Journal* while I’m in Asia.

We are excited about our mission in Southeast Asia. We are excited to teach people the fullness of the gospel of Jesus Christ, of which I bear a strong testimony. We are also excited about helping our missionaries to stay healthy and getting them the best possible care when problems come up. This won’t be easy — especially in places where medical care isn’t what we are used to. Now, I hope you’ll set a definite time for your mission — and go without letting the years slip by like we were doing with a “couple of years” moving timetable.

*Glen C. Griffin, M.D.*

EXECUTIVE EDITOR



*by* Elder Russell M. Nelson



# Called *to* Serve *and to* Save

---



Those of us with a wonderful eternal companion should be very thankful. Without Sister Nelson, I would not be what I am. You know that she is the mother of our 10 children and the grandmother of our 51 grandchildren. Less well known is the fact that she never murmured through the years of medical school, nor did she ever complain during many years of post-doctoral education and military duty that preceded later seasons of a more adequate income for our family.

Well, perhaps there was one exception. One night while we were strolling down Boylston Street in Boston, she pressed her nose against the window-pane of a furniture store and asked, “Do you think we will ever be able to afford a lamp?”

Few people know the importance of the encouragement she gave when I needed it most. In our early days in the pioneering of open-heart surgery, an operative fatality plunged me into the depths of depression and self-disdain. I was ready to quit. Sister Nelson, after listening patiently to my grieving, sternly said, “Stop feeling sorry for yourself. All that you have learned will be lost if you quit now. Get up and go to work! Go back to the lab! Learn more and work harder!”

Fortunately, I was wise enough to heed her counsel. Now you see why, without her, I would not be what I am or where I am. Even more important has been her refining spiritual influence upon me. She is still working on that project.

#### GREETINGS FROM LEADERS OF THE CHURCH

I bring greetings to you from President Gordon B. Hinckley, President Thomas S. Monson, President James E. Faust, and my brethren of the Quorum of the Twelve Apostles. Church membership is now 11 million, and congregations of Saints are established in more than 160 nations. The Church, with its increasing worldwide appeal, has become a phenomenal force for good across the earth.

#### LATTER-DAY SAINT PHYSICIANS

You are sustaining this broad pattern of global growth by your personal examples. We thank you most sincerely. In a very real way, each of us has been called to serve and to save. Service and salvation are fundamental objectives of our lives — whether at work, at home, or in the Church.

As associates in the Collegium Aesculapium — as Latter-day Saint doctors committed to serve and to save — you are special people. You are dedicated not only to the physical, but to the spiritual and ethical facets of medicine as well. Your lofty objectives are made even more difficult in these days when personal grooming of many doctors

and nurses is becoming increasingly casual. They prefer to “dress down” rather than to “dress up” for their duties. They tend to blend with the careless in the crowd instead of standing out as beacons of help and of hope. Do you wonder how people can respect doctors and nurses when they don’t look like doctors and nurses? Casualness can also be offensive to older patients when strange technicians and aides call them by their first names. This becomes another affront to a patient’s personal dignity — already in peril when illness strikes.

Gratefully we acknowledge exemplary physicians as rays of hope for patients who want to look up to their doctor with respect and trust. You are professionals who know the difference between a profession and a business and are committed to uphold that distinction. In contrast to the usual practice in commerce and trade, you freely teach and train your own replacements. Instead of restricting the free flow of knowledge by patents or secrecy, you teach without restraint. You know that your competition is not against other doctors, but against disease, suffering, and death. You lose yourselves in the service of others instead of seeking personal gain at the expense of others.

#### THE TWO GREAT COMMANDMENTS

To be a doctor is a unique privilege. Physicians are given the opportunity each day to spend the entire day striving to obey those two great commandments — to love God and to love their neighbors.

Striving to comply with the commandment to “love thy neighbour” begins at home. There we learn to love our closest neighbors and friends — members of our own family.

The first commandment is first because it is a prerequisite to compliance with the second. One can only understand the brotherhood of man if one first understands the fatherhood of God. These two commandments are never antagonistic; they are always synergistic.

Love of your spouse is richer, deeper, and more enduring if you first love God. Love for your children is kinder, more tender, and more compassionate if you first love God. Love for your patients is more sympathetic and competent if you first love God. And your professional knowledge will be magnified if you know and obey His irrevocable laws upon which all healing depends.

Those laws also require that some day we must leave this frail existence. God’s great plan of happiness mandates that each of us will ultimately fail as physicians, for all of our patients will eventually die. And one day, each of us will be numbered among that parade of patients who will pass through the gateway we call death to our own immortal life and glory.



## COVENANT OF CONSECRATION

Given these irrefutable realities, your life here will be richer, happier, and more meaningful as you develop your own alliance with God. Better yet, give yourself to the Lord. Surrender all of your selfish interests to His direction. Cultivate your own covenant of consecration. We read in the Pearl of Great Price how Enoch gathered together those who were willing to make covenants to serve the Lord. They covenanted to obey the celestial law, or the law of consecration. They were willing to give all that they had — even their lives — to building the kingdom of God. They became so righteous that they walked with God and He dwelt among them.

Consecration, catalyzed by faith and righteousness, promotes inner peace. Alma occasionally reflected his spiritual calm with expressions such as, “I ought to be content,” or “It mattereth not.” Consecration will immunize you from unrighteous pride, anger, hatred, and other forms of spiritual self-degradation.

A life consecrated to the Lord does not come naturally. Scripture teaches that “the natural man is an enemy to God, and has been from the fall of Adam, and will be, forever and ever, unless he yields to the enticings of the Holy Spirit, and putteth off the natural man and becometh a saint through the atonement of Christ the Lord, and becometh as a child, submissive, meek, humble, patient, full of love, willing to submit to all things which the Lord seeth fit to inflict upon him, even as a child doth submit to his father.” (Mosiah 3:19)

Called to serve and to save, you are magnetically drawn to the goal of salvation. To save a life, a limb, or a cherished relationship is much more rewarding than is the collection of a fee for service. When you promote spiritual as well as physical salvation, you find real joy, for “the spirit and the body are the soul of man.” (D&C 88:15) Components of the body are temporal, but spiritual elements are ageless, eternal, and essential to a fulness of joy.

## THE CHURCH — HOPE OF THE WORLD

Amidst the crunch of your crowded calendars, take time to reflect on the marvelous things that are occurring in our very own day. As members of the Lord’s church — called to serve and to save — we are the hope of the world, both temporally and spiritually. Consider some of the fruits of our labors:

- Humanitarian service has been extended to people in about 150 nations with nearly 3,500 projects. The Church has delivered tons of clothing, tons of food, tons of medical equipment, tons of books and other educational materials, and millions in cash. We have dug wells in African villages, fed people, and supplied them with clothing and shel-




---

“To save a life, a limb, or a cherished relationship is much more rewarding than is the collection of a fee for service. When you promote spiritual as well as physical salvation, you find real joy.”

ter. Thanks to faithful members who generously contribute fast offerings and funds for humanitarian aid, we are able to bring relief to people in need. Whether the emergency be a hurricane in Honduras, an earthquake in Taiwan, or a tornado in Salt Lake City, help comes from Saints who are eager to serve and to save.

- To provide places of worship throughout the world for our growing congregations, about 400 chapels are being constructed each year. Wherever they are located, our buildings and grounds are a credit to the community.
- Signs of spiritual progress are also evident. Five months ago, Sister Nelson and I were in Chile with President and Sister Gordon B. Hinckley. He reminded us that when he first came to Chile some 30 years ago, we might have had a hundred or so members there. But on this recent occasion we spoke to a congregation assembled in a large football stadium with more than 57,000 people in attendance. At the close of the meeting, they

waved white handkerchiefs to show their love and respect. It was an awesome sight.

- The Book of Mormon is either available or being translated in 71 languages. Temples are being built and dedicated at an unprecedented pace. Contact with our FamilySearch Internet Genealogy Service is being made by patrons throughout the world at a rate exceeding 7 million hits per day. Promises made by the Lord to Abraham, Isaac, and Jacob some 4,000 years ago are being fulfilled in our day, precisely as foretold by holy prophets.

#### CHALLENGES YET AHEAD

Yet we have much work to do. Let me give you an illustration. A couple of years ago, Sister Nelson and I were guests at a new theme park in Shenzhen, China, not far from Hong Kong. One section of the park was called “Windows of the World.” There we were transported on a little bus with an intelligent English-speaking Chinese guide. He ushered us through exhibits that portrayed the Tower of London, Paris and its Eiffel Tower, Washington, D.C., with its replicas of the White House and Capitol

---

The guide explained that the statue was erected to “a god of some kind.” I asked if he knew that it represented the Lord Jesus. He replied, “No — never heard of him.”



building, and so on. Then we came to the window of Rio de Janeiro in Brazil, with its miniaturized harbor and replications of Sugarloaf and nearby Corcovado — the peak crowned with a large statue of Jesus Christ. As the guide explained these sights, he mentioned that the statue atop the mountain was erected to “a god of some kind.” We were stunned! Later I asked him if he knew that the statue represented the Lord Jesus. He replied, “No — never heard of him.”

No doubt most of his countrymen would be likewise uninformed. Indeed, ours is the challenge to invite all to come unto Christ and to encourage them to adhere to that commitment. In this world where Christianity is a minority religion and where our church is a minority among that minority, ours is the solemn obligation to teach the saving gospel of Jesus Christ.

Our efforts are being blessed with success. An ancient prophecy is being fulfilled in our day. In that prophecy God said, “Righteousness will I send down out of heaven; and truth will I send forth out of the earth, to bear testimony of mine Only Begotten; his resurrection from the dead; yea, and also the resurrection of all men; and righteousness and truth will I cause to sweep the earth as with a flood, to gather out mine elect from the four quarters of the earth.” (Moses 7:62)

As members of the Lord’s restored Church, ours is also the responsibility to promote peace on earth and goodwill among all humankind. Ours is the responsibility to bless nations of the world with the power of the priesthood and the fulfillment of God’s ancient covenant with Abraham, Isaac, Jacob, and remnants of the house of Israel. We have been entrusted with the Book of Mormon — the tangible evidence that the time for the gathering of Israel has come.

While many members are the first generation of their families to join the Church, we marvel at the manifold blessings that come to faithful families who have endured to the 6th or 7th generations. Among them are some of the most righteous and philanthropic people of our day. No doubt many of you and your posterity already are or will be numbered among them. They and you are “among the noble and great ones who were chosen in the beginning to be rulers in the Church of God.” (D&C 138:55)

#### AN ETERNAL PERSPECTIVE

Eternal law merits an eternal perspective. That perspective teaches us that there are three great pillars of eternal truth. They are independent, yet, interrelated. Pillar one is the Creation — the creation of the earth and life upon it. Pillar two is the Fall — the fall of Adam and Eve. Pillar three is the Atonement — the Atonement of Jesus Christ.

Man and woman were first created in the image of God in a paradisiacal state. In that condition, they would not bring children into mortality without a physical change. Thus, the Creation required the Fall. Indeed, Adam (and Eve) fell that mortal men might be. But mortal beings could not return to the presence of their Father. The Fall, therefore, required the Atonement: “For as in Adam all die, even so in Christ shall all be made alive.” (1 Cor. 15:22) The Atonement allowed mortal bodies to become immortal. Therefore, the Atonement enabled the ultimate purpose of Creation to be accomplished — a fullness of joy for all God’s creations.

The Lord declared that His work and His glory was to bring to pass the immortality and eternal life of man. Immortality is a gift to all through the grace of Jesus Christ. Eternal life — life with our families and with the Lord — is contingent upon obedience to essential ordinances and covenants. The supreme purpose of the Creation — eternal life — is made possible by the Atonement. To phrase that statement in its negative form, if families were not sealed in holy temples, “the whole earth would be utterly wasted.” (D&C 2:3)

The purposes of the Creation, the Fall, and the Atonement all converge on the sacred work done in temples of The Church of Jesus Christ of Latter-day Saints. The earth was created and the Church restored to make possible the sealing of wife to husband, children to parents, families to progenitors, worlds without end.

This is the great latter-day work of which we are a part. That is why we have missionaries; that is why we have temples — to bring the fullest blessings of the Atonement to the faithful children of God. That is why we respond to our own calls to serve and to save. When we comprehend the Savior’s voluntary Atonement, any sense of sacrifice on our part becomes completely overshadowed by a profound sense of gratitude for the privilege of serving Him.

As one of the “special witnesses of the name of Christ in all the world,” I testify that He is the Son of the living God. Jesus is the Christ, our atoning Savior and Redeemer. His Church has been restored to bless God’s children and to prepare the world for the Second Coming of the Lord. I so testify and leave my love and blessing with you along with my deep expression of gratitude, in the name of Jesus Christ, amen.

---

*Elder Russell M. Nelson is a member of the Quorum of the Twelve Apostles of The Church of Jesus Christ of Latter-day Saints. He is a retired heart surgeon, with numerous honors and distinctions. This address was originally given to the Collegium Aesculapium on March 30, 2000.*







# Our Medical Mission on the Other Side of Town



*by Edmund C. (Ted) Evans, M.D.*

**Y**ou've probably thought about the idea of going on a mission someday. Good. It may seem a long time off when you'll say goodbye to your patients and turn in your clinic keys and hospital parking pass. But the reality is that the years, or months, before that day comes will likely fly by in a hurry. And the time to be thinking about and planning for your senior mission is now. Let me help you get excited about really doing it — going on a medical mission that is.

A medical mission? What's that? You may know that DuWayne and Alice Schmidt served a special kind of mission in Mongolia or that Jack and Winona Jensen served a special mission in the Philippines. Or maybe you know some of the 52 physicians and their wives who are presently serving medical advisory missions of one kind or another all over the world.

But a medical mission isn't always on the other side of the world. Dewey and Lorraine MacKay served in a medical advisory role for the southwest part of the United States while based in their St. George, Utah, home.

Gloria and I just completed three years of missionary service at Temple Square in Salt Lake City where we did a mixture of medical and general senior couple missionary service. For one and a half of these years I also served as a counselor in the mission presidency while providing primary medical care for the missionaries. Later my assignment was changed to be the medical advisor for two

missions. But whether your mission is on the other side of town, like ours, or on the other side of the world, I can promise it will be a great experience. It won't be easy — but it will be great.

My role in both missions was to provide primary care for the young missionaries and mainly consultative care for the senior couples. We held office hours in the small medical office of the south visitors center and also in a convenient Church meetinghouse, and we made house calls to see missionaries in their apartments.

The Temple Square Mission is the smallest mission in the Church; the entire mission comprises only 10 acres. All 180 sister missionaries live within one block of the Square. The Salt Lake Mission has over four million visitors each year. Last year it received 60,000 referrals for teaching by local missionaries when the visitors return home. Almost half of the missionaries we worked with were from countries other than the United States and Canada. We worked with wonderful young people who spoke over 40 languages from 68 countries. They had courage, conviction, and determination beyond belief.

The health issues I saw at Temple Square included many pre-existing problems, including 12 cases of positive tuberculin tests (nine from contacts in the missionaries' home countries, three from volunteer service in U.S. hospitals or teaching in a Russian colony in Oregon.) There were several cases of positive hepatitis B that were not symptomatic and another symptomatic hepatitis

C. There were some cases of parasites, *H. pylori*, GERD, ulcers, and many cases of irritable bowel syndrome. Four new cases of cancer were diagnosed: thyroid carcinoma, meningioma, Hodgkins, and prostate carcinoma. Obesity was a common problem that became uniformly worse with generous meals and reduced opportunity for exercise.

Among the 180 sister missionaries, many had gynecological problems including dysmenorrhea, oligomenorrhea, ovarian cysts, and endometriosis.

Serious dental problems in the foreign missionaries was a big challenge. Many came from areas where the only dental treatment was extraction. Several sisters had no chewing surfaces. One arrived with wooden dentures. In one year, Missionary Medical paid \$52,000 for dental care despite the fact that many local dentists gave their services at no cost or for a greatly reduced cost.

Psycho-emotional problems were the most common seriously disabling problems. Many missionaries had pre-mission symptoms that had never been recognized or treated. Some had been diagnosed but were not disclosed on the missionary application. Some had even been advised not to disclose these problems or they would “never get a mission call.” Sexual abuse, with its prolonged toll of psychological damage, was very common. This was especially so in countries with cultures of male dominance. Some of these sisters finally felt they were in a situation where they could talk about abuse. They were given much-needed help through LDS Family Services, a blessing they would not have received had they not served a mission. All but one of the missionaries who had an early release went home for mainly psychological reasons.

**But there were many examples of great courage** on the part of missionaries who endured serious medical problems. A sister from Tahiti with a destructive bone cyst of the jaw with a fracture and osteomyelitis missed less than two weeks of missionary work even though she had a titanium plate placed in her jaw, her jaws wired together for several weeks, as well as administering IV antibiotics to herself for three months. A sister who had surgery for thyroid carcinoma missed only one week of work. An elder with cystic fibrosis who had a pre-mission heart-lung transplant did very well with two brief hospitalizations. A sister from Russia who had Hodgkins lymphoma was treated with chemotherapy and radiation but rarely missed a day’s work. A sister with multiple sclerosis finished her mission — exhausted! Several elders with leukemia in remission worked hard and served well. Another elder who had hypertrophic cardio-myopathy required medications but did well.

Without medical advice and support, these young peo-

ple couldn’t have done it. Just think what a mission president without medical experience would do. The Church needs medical advisors, here and all over the world.

That’s why we served.

**You may wonder, “How did you prepare?”**

The answer to that question is very complicated and goes back several generations. Both Gloria and I have ancestors who joined the Church in its infancy. We have been raised on family traditions of service and sacrifice. From childhood we have thrilled to accounts of heroes who left homes and families, crossed the ocean, and struggled westward to join the prophet and the Zion of their dreams. One loving mother knew that she would not survive the trip and was buried at sea. Her family arrived in Nauvoo but her husband died while seeking work to get the needed equipment to cross the plains. Their eight orphaned children all made it to Utah. Others left beloved children in shallow graves along the trail. Even under these awful circumstances, many left their homes and families to serve missions. Others were called to leave their homes and take their families into unsettled, unknown places to serve colonizing missions. Some of these callings and assignments were desperately difficult. With all the adversities these people had, how could any of us not want to serve?

During our growing up years, we watched as many around us were called on missions. We were enchanted with their accounts of traveling without purse or scrip, sleeping in haystacks, and getting free meals from generous housewives. I was excited by accounts of missionaries escaping from Germany as World War II war clouds darkened. I was the third of five sons. My two older brothers had to go to war instead of serving missions. But immediately after the war, I was called to serve in the British Mission. This was a profoundly positive experience. Gloria shared my mission with me through weekly letters and ever since we have hoped and planned on serving a mission together sometime after our family matured.

When I returned from that mission I entered medical school, married Gloria during the 2nd year, and was a tour guide on Temple Square. In the years that followed, we lived in Minneapolis, Albuquerque, Los Angeles, and San Antonio during my residency and military service time. During those years we often had missionaries in our home; for a while it became a convalescent home for a sick missionary. The experience of living in small branches outside of Utah was very good for us and for our growing children.

Upon our return to Salt Lake City, I practiced pediatrics in a mixed group that had partners who were very active as bishops, as mission presidents, and in other Church callings. Humanitarian service was very much

honored among my partners. Working at Primary Children's Hospital and seeing children with special needs brought in from many countries as well as locally made me constantly aware of the medical needs of children. All these experiences engendered feelings of service. At one time I was stimulated to go to South America on a medical project. In the midst of trying to learn Spanish in preparation for this, I was called to be the bishop of our ward, which erased that opportunity.

Two of our three children who served missions developed medical problems that would have benefited greatly from the type of medical care that is now provided by our cadre of medical advisor missionaries who serve all over the world. One of our own sick missionaries was incorrectly diagnosed as having infectious mononucleosis when the problem was in fact gastro-intestinal parasites. Our daughter, who served in the Philippines, also had parasites that caused her to lose considerable weight, but an even bigger problem was that the disabling illness of her companion greatly interfered with their ability to teach the gospel. How grateful she was for comfort and support given by a wonderful senior couple who "saved her life" with love and reassurance. It would have been even better if she could have been treated for the parasites and given some nutritional guidance while on her mission instead of having to wait until she got home.

Also, knowing what we know now about rampant tuberculosis in many parts of the world, we wish that all missionaries had been skin tested on completion of their missions, which could have avoided some cases of tuberculosis passed on to families of returning missionaries.

Much has been accomplished in providing medical support to our missionaries in recent years, which has greatly decreased the "down time" of missionaries and their companions. Before an effective program of medical support was established, as many as 30% of our missionaries serving in underdeveloped areas were not functioning at any one time because of medical or emotional problems. Think of the substantial loss of missionary work that this was. Looking back 50 years ago to my own experience of being a 20-year-old district president dealing with some very serious medical problems gives me chills.

Those experiences made us very anxious to serve a mission together, but about 20 years ago we began having some health problems that made us wonder if our dream of a mission would ever happen. I was in an automobile accident with injuries that took several years to subside. Other medical problems saddened us as we thought these problems might eliminate us from service. While talking with President Gil Warner and his wife, Nedra, about a

call to the Family History Mission, President Warner suddenly looked up and said, "Ted, you are a doctor. They urgently need you at Temple Square." He picked up the phone, called President Lowell Snow, the president of the Salt Lake Temple Square Mission, and told us to hurry across the street to see him. President and Sister Snow looked at us as if we were manna from heaven. Their only question was, "When can you start?"

Our experience on Temple Square and later in the Salt Lake City Mission was one of the greatest experiences of our lives. In addition to the medical services that we provided, Gloria worked along with the sister missionaries at the information desks, at computers assisting patrons with Family Search<sup>®</sup>, and in the Legacy Theater in the Joseph Smith Memorial Building. She loved and comforted many of the sister missionaries as they had doctor and dental visits and as they suffered illnesses, homesickness, discouragement, and anxiety about going home to difficult situations. We were part of their zones and districts, enjoyed their prayer meetings and training sessions, and at times experienced the joy of having them in our home. We shared countless hugs, some tears, and many smiles. And after they went home many have kept in touch with letters and a flood of wedding invitations. These young missionaries have become a part of our family and we feel that we have earned a place in their hearts. They have given us much more than we have given them.

The beneficial effect of our mission on our children and grandchildren has been another almost unexpected blessing. Our whole family became interested in our mission. Many came to mission activities, often bringing their little children with them. How pleased we were to have them enjoy our mission with us. We are convinced that our experience will help our grandchildren become more excited about serving missions themselves. So the blessings of our mission extended way beyond the ones we received.

We loved our mission so much that the hardest part of the mission was the day that we could no longer wear our mission badges.

As I was approaching retirement age, a very wise man gave me some profound and sage counsel, saying, "It is not what you retire from that matters... it's what you retire to." We cannot think of any greater retirement than providing medical care and counsel to the wonderful young people who are serving the Lord as missionaries.

---

*Ted C. Evans, M.D. and his wife Gloria recently completed a 3-year medical mission at Salt Lake City's Temple Square. Ted is a retired pediatrician.*



# A Beautiful Experience



*by Gloria T. Evans*

**O**ur mission was one of the most beautiful experiences I've ever had in my life. The privilege of serving there — the joy that it was — is almost more than I can put into words. The young women we have met from all over the world are the pioneers of the 21st century in their own homelands. They are incredible!

My main missionary duty was to help my husband, Ted, with the health care for the sisters. On occasion I drove them to medical appointments, including surgery, trying to take the place of their mothers. I felt it a deep responsibility to have these precious sisters in my car and be trusted with their safety — but I'm grateful to Father in Heaven because we had no problems — no accidents, no injuries. We had safety in our travels.

One medical experience especially stands out in my mind. A dear sister from Japan was referred to a consultant for an evaluation including ultrasound. Because of severe language difficulties she and her doctors had trouble communicating. She spoke enough English to give tours and answer mission-related questions, but she was not able to give the doctor any useful medical information. It became critical. As I sat with this dear sister I knew we needed help. Somehow she had to tell us. Mercifully, the gift of tongues can come to ordinary people like us, when it is necessary. Suddenly she understood what I was asking her. Even more miraculously, I understood what she was telling me. Then it dawned on me...this was the answer! I ran to the doctor's office and said, "Oh, she told me...she has told me." Every time I think about that I almost weep with gratitude.

There was a sister from West Africa whose horrendous experiences are indelibly etched into my brain. She arrived at Temple Square with practically nothing. She came from an area where there has been war and rebellion. The rebels had been terrorizing the townspeople. They killed her father and her brother. These rebels cap-

tured her sister and forced her to suffer the amputation of her hands. Our missionary barely escaped losing her own hands. This African sister rarely heard from home. Her mother lives too far from a city to be able to send mail. Her branch president could only write a letter every three months with the news of her family.

The war and rebellion continued to rage during her mission. How could she not be anxious and worried? I asked her, "Sister, how can you possibly have any peace in your heart when your family is in so much danger?" She said to me, "Seeestuh Eeeevahins [I love the way she pronounced my name], I am happy. I must be happy. I am here."

Several years ago, when Pres. Hinckley traveled to Africa, he told the people a temple would be built in Accra, Ghana. However, there has been opposition to the construction of that temple. Less than six months after our African sister arrived, a member of the parliament of Ghana came to Temple Square. Our sister was asked to take him on a tour. Soon on the shoulders of this sweet, humble sister, who was spared from the rebel swords, knives, and machetes, rested the crucial task to give this government official a favorable impression of the Church and our temple. I watched her walk with him around the Square. I knew that because she was there, he had come. God had arranged it. I know she helped the cause of the temple in Ghana.

One afternoon I drove our African sister to the dentist for wisdom teeth extraction. On the way home she slept with her body relaxed and her hands folded peacefully in her lap. I glanced at her hands and beautiful long black fingers. There were no ugly stumps where hands should be. She was whole and beautiful. Words cannot express the overwhelming gratitude I felt that day to our merciful, loving Father in Heaven. I am filled with thankfulness for the joy and privilege of serving my mission in that beautiful place, Temple Square.



Temple Square sisters from all over the world greet visitors. (Top left, from Switzerland; top right, from Arizona; right, from Kenya; below, both from Japan.)



Elder and Sister Evans, here with Sister Shu-Huei Huang of Taiwan.



# COX-2 Inhibitor Drugs

---

*The Future of Pain and  
Inflammation Therapy*

*by* Kenneth J. Hunt, MSII  
Bruce H. Woolley, Pharm.D.

A preponderance of health concerns — from an elbow scrape to cancer — involve **some level of pain**. Thus, it was predictable that medical science would make strenuous attempts to decipher the **mechanisms** behind the feelings of pain and develop a means to alleviate it. Indeed, “**Take two aspirin and call me in the morning**” is one of the oldest medical clichés, but the phrase may be **more relevant** to pain management associated with various medical conditions than previously imagined.



**I**t was nearly 2,400 years ago when Hippocrates was the first to record the use of willow bark on patients to reduce fevers and pain. As medical science developed through the 18th century, it was discovered that willow bark contains salicylate, the same active ingredient found in modern aspirin. Half of a century later, salicylate was chemically isolated by French scientists and a crude form of acetylsalicylic acid was created in 1853 (See Table I: Timeline).

Acetylsalicylic acid was named “Aspirin” by Bayer in 1899 and has been marketed for the relief of pain and fevers ever since. In 1971, Sir John Vane discovered that aspirin irreversibly inhibits the cyclooxygenase enzyme of guinea pig homogenates.<sup>1</sup> A short time later, Smith and Willis reported similar findings in human platelets. The birth of non-steroidal anti-inflammatory drugs (NSAIDs) had occurred, defining a class of agents that exert both anti-inflammatory and undesirable side effects by inhibiting prostaglandin synthesis.

A little more than a decade ago, a more attractive paradigm emerged in the discovery of a second cyclooxygenase isoform. In Daniel Simmons’ biochemistry research laboratory at Brigham Young University, researchers discovered in 1991 that two cyclooxygenase enzymes existed. These were dubbed COX-1 and COX-2. The first enzyme, COX-1, is a consistent, physiological “housekeeper”<sup>2</sup>, while COX-2 was determined to be an inducible isoform, expressed in response to inflammatory stimuli. Simmons (*photo, this page*) was also instrumental in the elucidation of the mechanism of each enzyme and collaborated with pharmaceutical companies as they developed drugs that specifically inhibit the recently discovered COX-2 isoform.

It did not take long before pharmaceutical companies developed medications which would selectively inhibit the COX-2 enzyme while leaving COX-1, the housekeeping catalyst, relatively unimpeded. Two synthetic COX-2 inhibitors, celecoxib (Celebrex) and rofecoxib (Vioxx) were approved in 1998 and 1999, respectively. This began a new era in NSAID therapy and the drugs quickly became the most widely prescribed anti-inflammatory medications in the United States.

#### BIOLOGY OF COX-2 INHIBITION

The two cyclooxygenase enzymes share a 60% homology in their amino acid sequence. They catalyze the first two committed steps in the synthesis of prostaglandins from arachadonic acid (see Figure 1). The two isoforms are the products of distinct, single-copy genes located on chromosomes 9 and 1. The COX-2 gene product is much less stable than that for COX-1, consistent with the role of the former as an inducible, transient product and the

**TABLE I: TIMELINE OF COX-2 HISTORY**

400 BC	Hippocrates uses willow bark on patients to reduce fevers and pain.
1828	The active ingredient in willow bark, salicin, is chemically separated.
1839	Salicylic acid is synthesized from salicin
1897	Salicylic acid modified to Acetylsalicylic acid to make it less harsh on the stomach
1899	Acetylsalicylic acid is named Aspirin by Bayer.
1917	Bayer's patent on Aspirin runs out, allowing other companies to sell acetylsalicylic acid.
1971	British pharmacologist John R. Vane discovers aspirin's mechanism of action — that it inhibits the production of prostaglandins.
1982	Sir John R. Vane is co-winner of the Nobel Prize in Medicine for his discoveries concerning prostaglandins.
1990	Studies show regular use of aspirin may reduce risk of colon cancer.
1991	Researchers at BYU discover the COX-2 isoform of cyclooxygenase
1998	Celecoxib is approved by the FDA for arthritis treatment
1999	Rofecoxib is approved by the FDA



*Dr. Daniel L. Simmons, professor in Brigham Young University's Department of Chemistry and Biochemistry, led a team which discovered the existence of the COX-1 and COX-2 enzymes in 1991.*



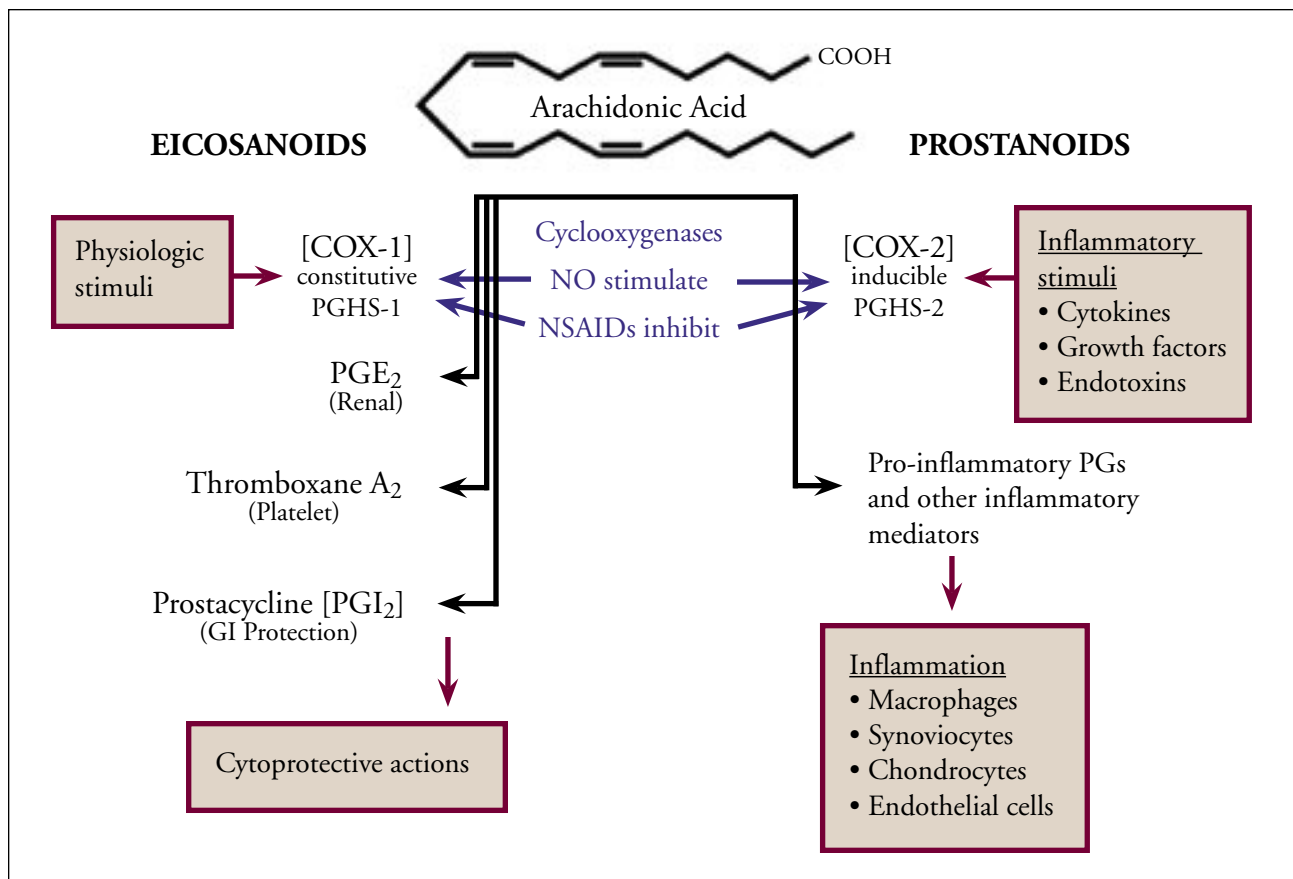


Figure 1

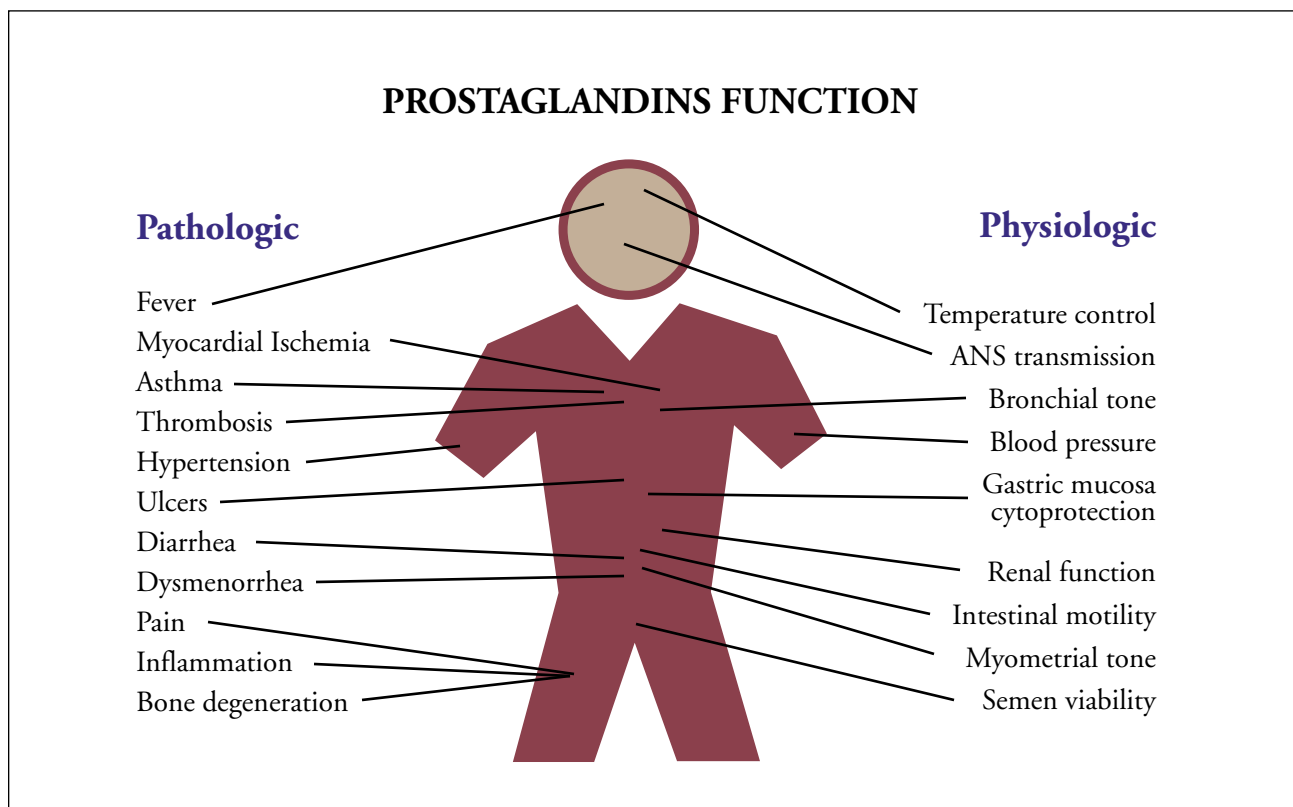


Figure 2

latter as a consistent, “housekeeper” involved in physiologic homeostasis.

COX-1 is constitutively expressed in virtually all tissues, most notable platelets, endothelial cells, the gastrointestinal tract, and the kidney. COX-2, on the other hand, is typically almost undetectable in most tissues under normal conditions, but is expressed in many cell types, including macrophages, fibroblasts, chondrocytes, epithelial, and endothelial cells when stimulated by inflammatory mediators<sup>3</sup>. The principle that has emerged from these observations is that COX-1, by virtue of its basally transcribed, stable message, functions as a “housekeeping gene” in the regulation of normal homeostatic functions, such as maintaining gastric mucosal integrity, platelet function, and renal blood flow. COX-2, which is rapidly induced and tightly regulated, participates in pathological and inflammatory tissue processes (see *Table II: COX isoforms*).

COX-2 INHIBITORS VERSUS TRADITIONAL NSAIDS

The common side effects of NSAID therapy include injury to the gastrointestinal mucosa via both local irritation and systemic effects mediated by inhibition of gastric mucosal cyclooxygenase. Prostaglandins protect mucosal integrity by stimulating secretion of mucus and bicarbonate, maintaining mucosal blood flow and promoting epithelial cell proliferation. Mucosal prostaglandins are synthesized by the constitutive COX-1 isoform of cyclooxygenase (see *Figure 2: Prostaglandins Function*). There is a growing body of data to suggest that the use of COX-2 inhibitor drugs results in fewer of the undesirable side effects that are associated with traditional NSAIDs.

Several short- and long-term studies<sup>4-8</sup> have demonstrated that there is a reduced risk of gastropathy and GI side effects with the use of COX-2 inhibitor drugs versus traditional NSAIDs. In patients with risk factors for NSAID gastropathy (e.g., advancing age, previous history of GI bleeding, concurrent use of anti-coagulant therapy,

prednisone, or other NSAIDs), COX-2 selective drugs are preferred. It remains to be seen whether or not COX-2 drugs will be free of renal toxicities, but results to date indicate that they are better tolerated than traditional drugs in this regard as well (see *Figure 3: NSAID Selectivities*).

INDICATIONS FOR COX-2 INHIBITORS

As pain is such a far-reaching complication of most illnesses, there is reason for medical research teams to explore various uses for COX-2 inhibitors. The initial research was performed using osteoarthritis, rheumatoid arthritis and dental pain models. Clinical trials with these models found celecoxib to be as effective as naproxen and aspirin, with significantly fewer adverse side effects. In addition, more than a dozen randomized, placebo controlled clinical trials over the past two years have demonstrated that the COX-2 selective inhibitors are as effective at treating the pain and inflammation associated with osteoarthritis as traditional NSAIDs. The new agents are also consistently better tolerated than traditional medications.

RHEUMATOID AND OSTEOARTHRITIS

Clinical trials have been conducted comparing NSAIDs to COX-2 selective inhibitors in the treatment of both osteoarthritis (OA) and rheumatoid arthritis (RA) pain. OA is the most prevalent type of arthritis, particularly in adults 65 years and older. OA is a chronic degenerative disease of the joints that frequently leads to chronic pain and disability. With the aging of our population, this condition is becoming increasingly prevalent and its treatment an increasing financial burden (see *Figure 4: Economic Impact*).

RA, on the other hand, is a chronic inflammatory condition in which the body’s immune system attacks cartilage and bone, usually causing joint disease. More than six million Americans suffer from this potentially debili-

**TABLE II: CYCLOOXYGENASE ISOFORMS**

<i>COX-1</i>	<i>COX-2</i>
<ul style="list-style-type: none"> <li>• Constitutive</li> <li>• Produced in most tissues</li> <li>• Hydrogen bonding — instantaneous, reversible</li> <li>• Responsible for protective functions (renal, vascular, platelet, gastric mucosa)</li> </ul>	<ul style="list-style-type: none"> <li>• Inducible</li> <li>• Produced in inflammatory &amp; immune cells (fibroblasts, endothelial cells, macrophages, neutrophils, mast cells)</li> <li>• Covalent bonding (time dependent, irreversible)</li> <li>• Responsible for proinflammatory</li> </ul>

The COX isoforms are 60% homologous and are encoded on chromosomes 9 and 1 respectively.



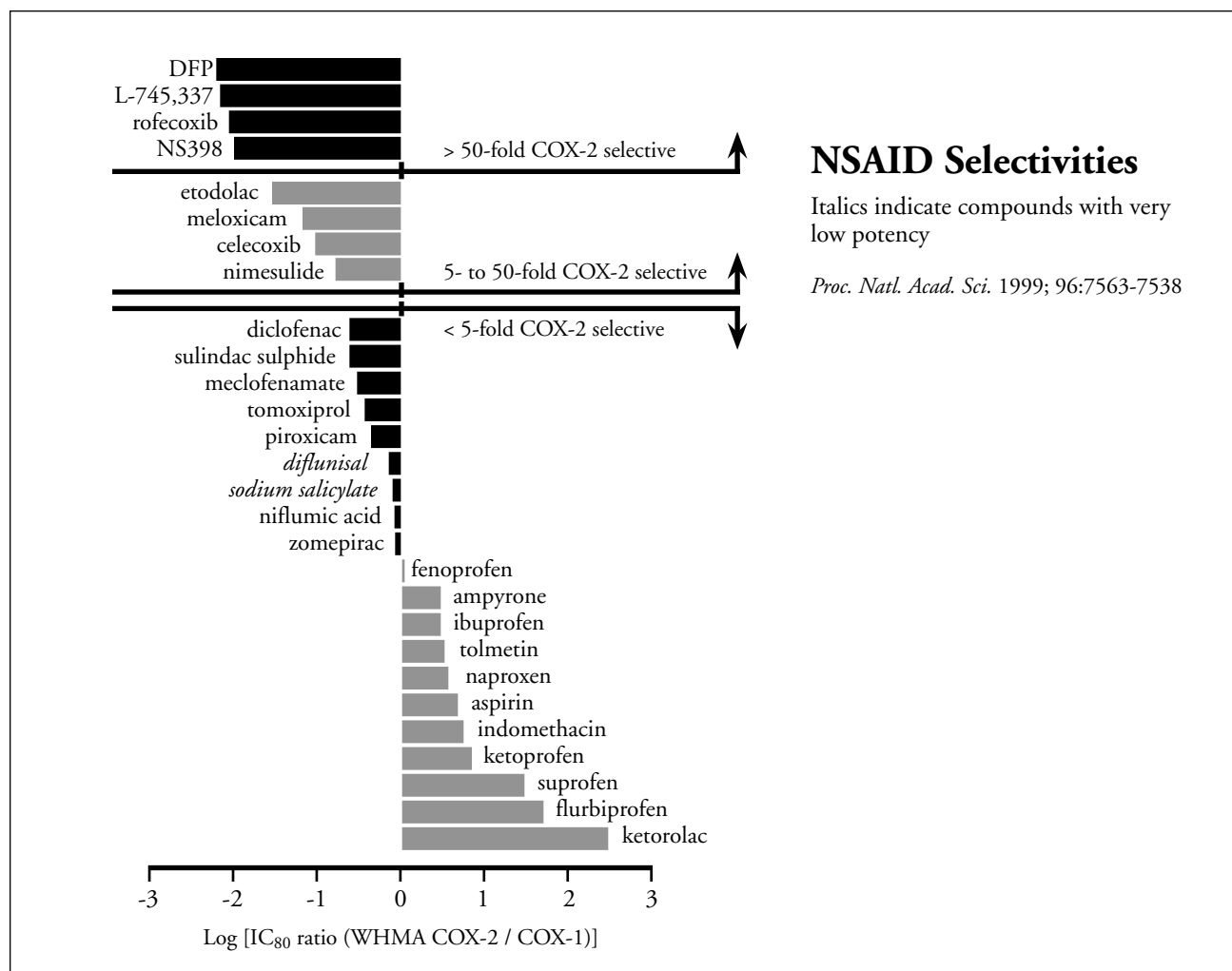


Figure 3

tating disease and most of them are women. Though the disease tends to be self-limiting, it follows a painful course of degeneration. Treatment of the pain associated with both of these types of arthritis has become a subject of great interest, particularly in trials involving the COX-2 inhibitors.

Celecoxib and rofecoxib have both been compared to traditional NSAIDs including ibuprofen, naproxen, and diclofenac for the treatment of osteoarthritis and rheumatoid arthritis. These reports consistently demonstrate that the COX-2 specific inhibitors are comparable to NSAIDs and superior to placebo by a statistically significant margin in relieving joint pain. Additionally, studies have been published focussing on gastrointestinal side effects associated with the COX-2 inhibitor drugs. These reports indicate that celecoxib and rofecoxib are better tolerated than traditional NSAIDs and are associated with significantly fewer gastro-intestinal side effects, such as gastropathy, ulcers and bleeding.

COX-2 INHIBITORS AND COLORECTAL CANCER

In 1999, approximately 130,000 new cases of colorectal cancer were diagnosed in the United States to go along with more than 57,000 colorectal cancer-related deaths. The majority of these patients are over 50 years of age. This type of cancer remains the second most common cause of cancer death in this country and is associated with greater cost due to hospitalization than any other

**TABLE III: RISK FACTORS FOR COLORECTAL CANCER**

- Age older than 50 years
- History of colorectal adenomas
- History of breast, ovarian, or uterine cancer
- Family history of colorectal cancer
- Family hereditary syndromes (FAP, HNPCC)

cancer.<sup>9</sup> Worldwide, there are more than 850,000 new cases of colorectal cancer diagnosed each year and more than half a million deaths (see Table III: Risk factors).

As colorectal cancers have become an important health concern and take a period of years to develop, tumor prevention and screening has become an area of great interest. Past epidemiologic data suggest that aspirin may have a role in reducing the incidence of polyps by 40-45%.<sup>10</sup> As the Pandora's box of COX-2 research evolved in the late 1990s, much attention was focused on the enzyme's expression in the GI tract.

Under normal physiologic conditions, COX-2 is expressed at undetectable levels in the GI tract, but this expression rises by up to 50 fold in the presence of colorectal malignancies.<sup>11</sup> It was discovered that this increase in COX-2 expression affects tumor number in patients with colorectal tumors. Research involving COX-2 inhibitor drugs demonstrated that these agents reduce tumor number, making them a relevant target for prevention and treatment of colorectal cancers.

Researchers in this area are currently attempting to elucidate the mechanism of colon cancer prevention with these new agents. Specific COX-2 inhibition has been shown to decrease the formation of tumors in experimen-

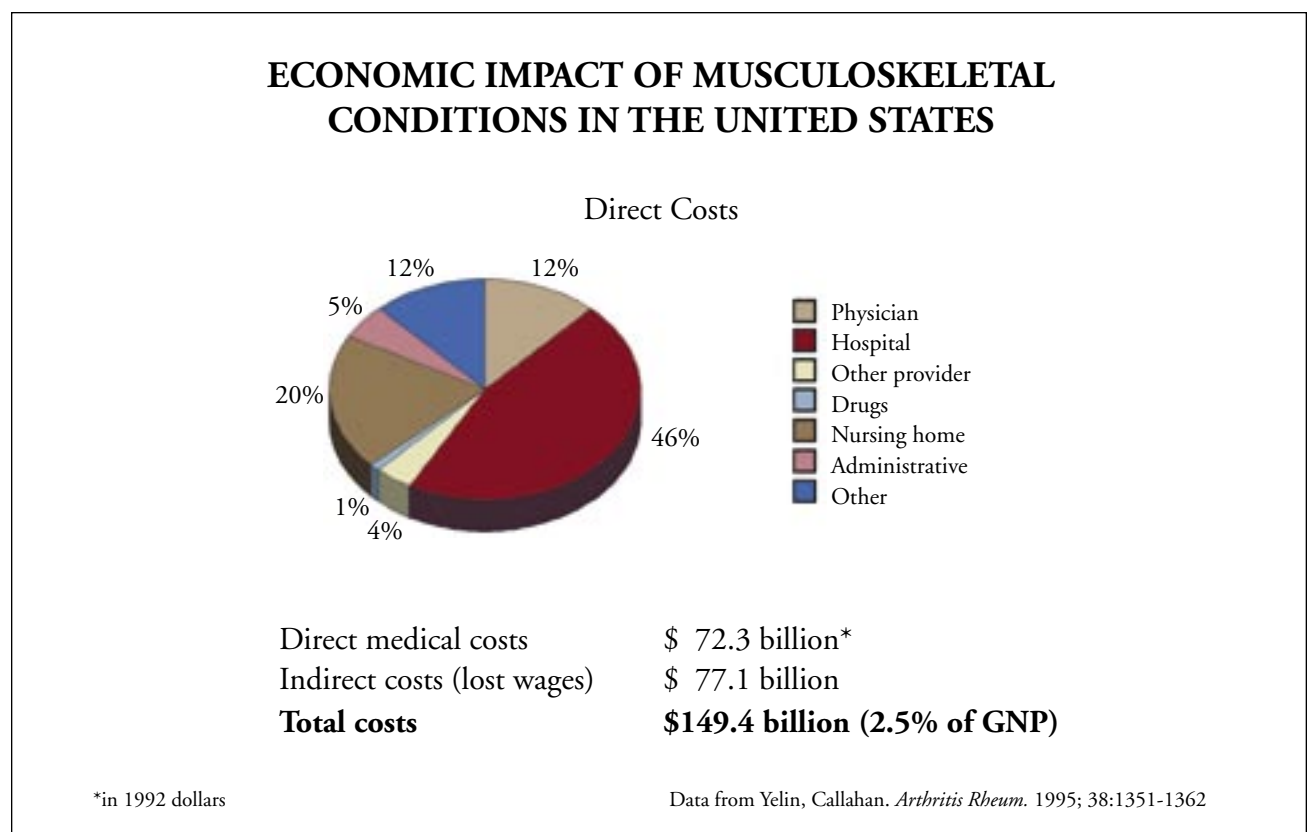
tal models of colonic tumorigenesis.<sup>12</sup> COX-2 activity has also been demonstrated to inhibit apoptosis in both human colonic cancer-derived cell lines and FAP polyps. Inhibition of this enzyme has been associated with an increase in this form of programmed cell death.<sup>13</sup> This observed induction of apoptosis likely contributes to the chemopreventive action of COX-2 inhibitors.

Data on the role of COX-2 inhibitors in human colorectal cancer prevention are limited because of the short time that these drugs have been available. Preliminary data from a small cohort of FAP patients taking celecoxib (a COX-2 inhibitor) for 6 months, however, have demonstrated a 28% reduction in the number of adenomatous polyps.<sup>14</sup> Though more data are required before specific recommendations are made, COX-2 specific inhibitors show promise in colorectal cancer prevention and treatment.

ALZHEIMER'S DISEASE

The role of prostaglandins in mediating fever has long been appreciated. There is epidemiological evidence that nonsteroidal anti-inflammatory drugs reduce the incidence and may provide therapeutic benefit in patients with Alzheimer's disease. Autopsy examination of the

Figure 4



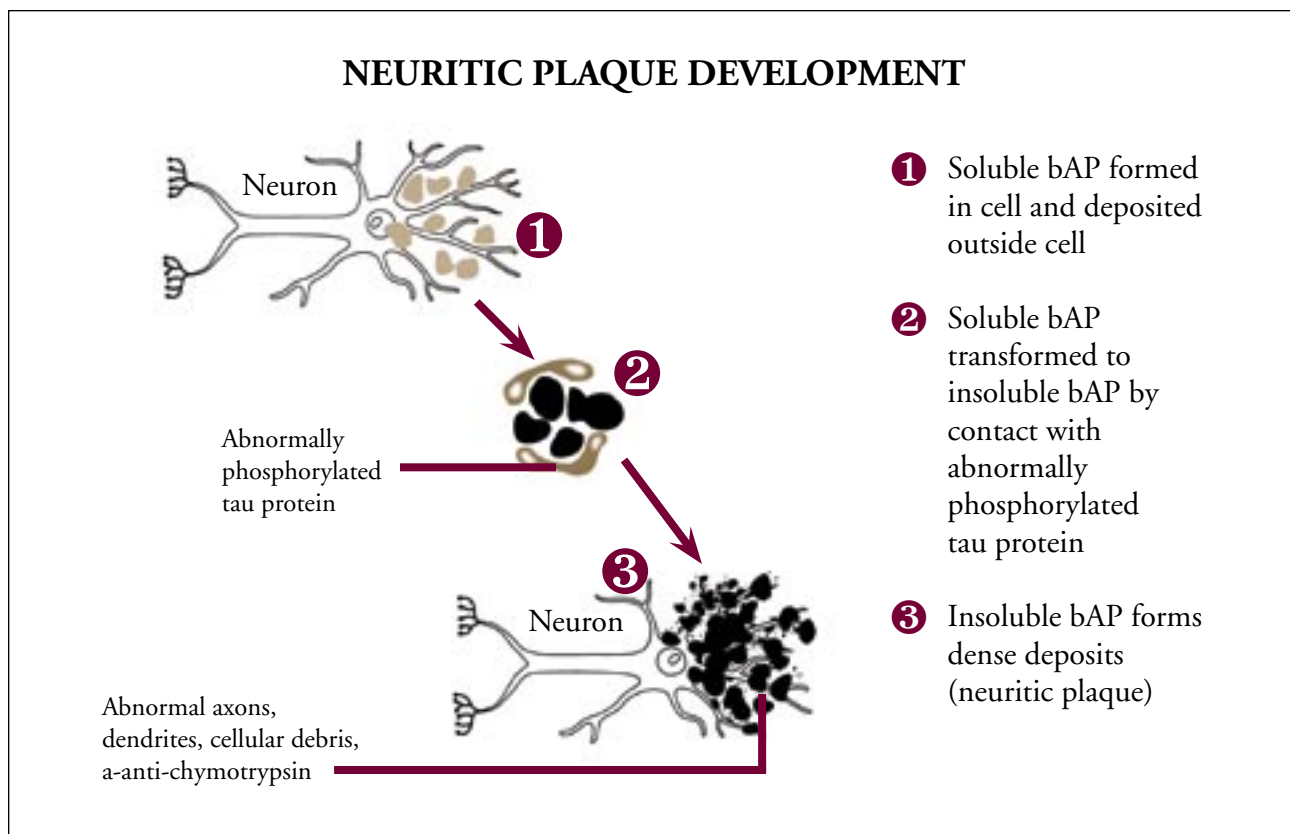


Figure 5

brains of patients who passed away with Alzheimer's disease reveal increased expression of COX-2 protein at sites of amyloid plaque (see Figure 5: *Alzheimers plaques*). Clinical trials with specific COX-2 inhibitors are under way. COX-2 expression may play a role in the development of Alzheimer's disease, although it should also be noted that NSAID therapy has been associated with decreased cognition, particularly in the elderly. In a recent study<sup>11</sup> of individuals over 65, moderate doses of NSAID therapy was associated with significant longitudinal memory loss.

Emerging research evidence suggests that the COX-2 enzyme is expressed constitutively in the developing brain, playing a role in their proper maturation and function. COX-2 expression may also be up-regulated at certain sites, including the the microglia of cognitive centers within the hippocampus and cortex in Alzheimer's disease.<sup>15</sup> On the basis of the elevated expression of COX-2 in Alzheimer's disease, COX-2-specific inhibitors may find clinical utility in the prevention or treatment of this condition. The seemingly optimistic outlook for this future use of COX-2 inhibitors is not entirely certain as most of the findings supporting this perspective are based on in vitro and in vivo models and must be rigorously corroborated in human studies before conclusions can

be made.<sup>16</sup> Some of these trials are already planned or underway.

#### CLINICAL AND TREATMENT IMPLICATIONS

Studies available thus far support the hypothesis that selective COX-2 inhibition will achieve comparable efficacy with less toxicity than conventional nonselective NSAIDs.

As this is a relatively new drug class, however, long-term studies of gastrointestinal mechanisms and side effects are necessary before the true safety of the COX-2 agents can be definitively ascertained. The prevalence of ulcers in patients on long-term NSAID therapy is about 20%, and the annual incidence of serious complications from these ulcers is 1-4%. The critical question is whether selective COX-2 agents will significantly reduce the incidence of serious GI events related to ulcers in patients requiring NSAID therapy, and/or reduce the associated costs and mortality rates, associated with such events.

#### *Which Patients Will Benefit?*

The current FDA labeled uses for celecoxib include familial adenomatous polyposis (FAP), osteoarthritis and

rheumatoid arthritis. Rofecoxib is approved for dysmenorrhea, osteoarthritis, and acute pain. Theoretically, any patient requiring chronic NSAID therapy for management of arthritis or the prevention of colorectal cancers will probably benefit from COX-2 selective inhibitors. However, groups of patients who are at higher risk for serious GI events from NSAIDs are the most obvious candidates for COX-2 specific agents. These specific groups include the elderly, those with documented prior ulcers, and patients on concomitant steroids. Benefit will also be seen in patients who have one or more risk factors for colorectal cancers as listed above.

In treating patients who are not in the high risk category for serious GI events from NSAID-associated ulcers, cost is another important factor in deciding whether to prescribe a selective COX-2 agent versus a conventional NSAID, since the latter are considerably less expensive and will likely be so for some time. The addition of a proton pump inhibitor to dyspeptic patients on conventional NSAIDs may negate this cost advantage, although dyspepsia may also occur in patients receiving selective COX-2 agents as well, even without the formation of ulcers.

#### *Patients with Renal Insufficiency*

The clinical trials of COX-2 inhibitors to-date have not included patients with abnormal renal function. Thus, the safety of these agents in patients with elevated creatinines is unknown. COX-2 may also play a physiological role in the regulation of salt and water balance

by the kidney. Further work is required in this area prior to any recommendations are made for patients with renal insufficiency. We do know, however, from clinical trials in patients with normal renal function that COX-2 inhibitors do not cause elevation of creatinine.

#### *COX-2 and Surgical Pain Relief*

The absence of effect of the specific COX-2 inhibitors on platelet aggregation would suggest that they could probably be administered safely to patients up until the time of surgery. The long-term safety of COX-2 inhibitors in patients taking anticoagulants remains to be determined.

There is, however, some light in the FDA pipeline. Parecoxib, the first investigational injectable COX-2 specific inhibitor, is in clinical trials for surgical pain management. In a study of 202 postgynecological surgery patients, parecoxib was more effective in the control of pain than a 4 mg dose of the injectable narcotic analgesic morphine, and similar in efficacy to ketorolac, a non-steroidal anti-inflammatory drug (NSAID). The study included multiple centers, including LDS Hospital in Salt Lake City. Injectable analgesics are generally preferred in the pre-operative setting because they have a fast and reliable onset of action, and can be administered before, during, and after surgery regardless of a patient's ability to swallow.

Injectable analgesics currently available in the United States are limited to narcotics and NSAIDs and are associated with significant adverse effects. Parecoxib sodium is

**TABLE IV: SAFETY QUESTIONS**

• Safe in presence of GI inflammation? <i>COX-2 induced in H pylori gastritis and IBD</i>
• Retard ulcer healings? <i>COX-2 induced with gastric injury and ulcer rims</i>
• Cause ulcers in subgroups? <i>Patients with erosions more likely to develop ulcers</i>
• Cause fluid retention, induce renal failure? <i>COX-2 expressed constitutively in kidney</i>
• Alter ovulation? <i>COX-2 cyclical induction, uterine important for labor onset</i>
• Induce vascular disease? <i>COX-2 sustains vascular protacyclin production</i>

Adapted from: Hawkey, Lancet 1999. 353:308

the first investigational injectable COX-2 specific inhibitor and targets the COX-2 enzyme, which becomes activated at sites of injury, including surgical incisions.<sup>17</sup> Compared with conventional NSAIDs such as ketorolac, COX-2 inhibitors are less likely to cause GI ulceration or reduced blood clotting.

#### THE FUTURE OF PAIN RELIEF

The development of selective COX-2 inhibitors has been an exciting advance in the management of pain and inflammation and holds great promise in other areas. Clinical trials have convincingly demonstrated that celecoxib and rofecoxib induce very few gastrointestinal complications compared to conventional and non-selective NSAIDs. However, the well known contraindications for NSAIDs, such as late pregnancy, aspirin-induced asthma, congestive heart failure and renal dysfunction, will also apply to the COX-2 inhibitors until it is otherwise proven by research trials. In a recent article in the *Lancet*, Hawkey delineates various safety issues that will need to be addressed in future trials (*see Table IV: Safety Questions*).<sup>18</sup>

In contrast to the traditional and non-selective NSAIDs, COX-2 inhibitors may provide an insight into additional therapeutic areas, such as colorectal cancers and Alzheimers dementia, where the potential relevance to COX-2 mechanisms are currently being explored and clinical trials being performed. With the rapid clinical acceptance of celecoxib and rofecoxib, knowledge about their clinical usefulness in various inflammatory disease states and pain disorders is expanding dramatically. For the many patients suffering from such conditions, the selective COX-2 inhibitors are likely to become a significant addition to the therapeutic arsenal of analgesic and anti-inflammatory drugs.

---

*Kenneth J. Hunt is a second-year medical student at the University of Utah School of Medicine. Bruce H. Woolley, PHARM.D., is a professor of nutrition at Brigham Young University, as well as a nationally recognized lecturer on therapeutics.*

#### REFERENCES

1. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol.* 1971 Jun 23;231(25):232-5.
2. Vane JR; Bakhle YS; Botting RM Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol*, 1998, 38:, 97-120
3. Amin AR, Vyas P, Attur M, et al. Superinduction of cyclooxygenase-2 activity in human osteoarthritis-affected cartilage. *J Clin Invest.* 1997;99:1231-7
4. Day R, Morrison B, Luza A, et al. A Randomized Trial of the Efficacy and Tolerability of the COX-2 Inhibitor Rofecoxib vs Ibuprofen in Patients With Osteoarthritis *Arch Intern Med.* 2000 Jun 26;160(12):1781-1787
5. Cannon GW, Caldwell JR, Holt P, et al. Rofecoxib, a Specific Inhibitor of Cyclooxygenase 2, With Clinical Efficacy Comparable With That of Diclofenac Sodium: Results of a One-Year, Randomized, Clinical Trial in Patients With Osteoarthritis of the Knee and Hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum.* 2000 May;43(5):978-87
6. Ehrlich EW, Schnitzer TJ, Mellwain H, et al. Effect of Specific COX-2 Inhibition in Osteoarthritis of the Knee: A 6 Week Double Blind, Placebo Controlled Pilot Study of Rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group *J Rheumatol.* 1999 Nov;26(11):2438-47
7. Bensen Wg, Fiechtner Jj, Mcmillen Ji, et al. Treatment of Osteoarthritis With Celecoxib, a Cyclooxygenase-2 Inhibitor: A Randomized Controlled Trial. *Mayo Clin Proc.* 1999 Nov;74(11):1095-105
8. Hawkey C, Laine L, Simon T, et al. Comparison of the Effect of Rofecoxib (a Cyclooxygenase 2 Inhibitor), Ibuprofen, and Placebo on the Gastroduodenal Mucosa of Patients With Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. The Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. *Arthritis Rheum.* 2000 Feb;43(2):370-7
9. Levin B, Mocharnuk R. Cox-2 Inhibitors and Cancer Chemoprevention. *Medscape Pharm.* <http://www.medscape.com/medscape/oncology/treatmentupdate/2000> November 26, 2000.
10. Giovannucci E, Egan KM, Hunter DJ, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med.* 1995;333:609-614.
11. Kargman S, Charleson S, Cartwright M, et al. Characterization of prostaglandin G/H Synthase 1 and 2 in rat, dog, monkey, and human gastrointestinal tracts. *Gastroenterology.* 1996;111:445-454.
12. DuBois RN, Radhika A, Reddy BS, Entingh AJ. Increased cyclooxygenase-2 levels in carcinogen-induced rat colonic tumors. *Gastroenterology.* 1996;(110):1259-1262.
13. Smalley W, Ray WA, Daugherty J, Griffin MR. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. *Arch Intern Med.* 1999;159(2):161-166.
14. Gottlieb S. COX 2 inhibitors might be useful in cancer prevention. *Br Med J.* 1999;319(7218):1155.
15. Lipsky PE *Am J Med.* 1999 May 31;106(5B):51S-57S.
16. Saag KG, Rubenstein LM, Chrischilles EA, Wallace RB. Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. *J Rheumatol.* 1995 Nov;22(11):2142-7.
17. Jain KK. Evaluation of intravenous parecoxib for the relief of acute post-surgical pain. *Expert Opin Investig Drugs* 2000 Nov;9(11):2717-2723
18. Hawkey CJ. COX-2 inhibitors. *Lancet.* 1999 Jan 23;353(9149):307-14.



NEW TREATMENTS  
FOR AGING SKIN

RICHARD W. PARKINSON, M.D.



**W**hen President David O. McKay was 90 years old he quipped that growing older was a terrible thing, but he preferred it to the alternative.

Aging is terrible in some ways, difficult in many ways, and challenging in most ways. Among the myriad challenges we confront as we age, perhaps none is greater than looking at ourselves in the mirror. Gray hair, or no hair at all, wrinkles, sags, blotches and bags, are all painful to behold, and right there in plain view — if we happen to be wearing our bifocals.

For most of us, growing older means looking the part, which includes every unsightly change brought about by tired genes, the sun, a diet rich in sugar and fat, ignoring the Word of Wisdom, gravity, and our general aversion to exercise. No tissue in the body is more adept at showing its age than the skin, and every mile of it is on display. Until recently there was little you could do about the effects of aging to your skin. However, thanks to new discoveries and new technologies, aging skin can now be rejuvenated, or more appropriate in severe cases; resuscitated.

Though inner beauty is more important than outer beauty, our narcissistic culture entices us to spend a great deal of time and money on our looks. For example, Americans spend more money on cosmetics than on cancer research. Before condemning ourselves, consider the case of the elderly woman I cared for last year. Though dying of cancer, more concern was directed toward a wart on her nose than her impending mortality. Was her concern with her appearance overly vain? Just what does it mean to “grow old gracefully?”

We all know people who look either younger or older than they really are. Why are some lucky and others not? Obviously, living a righteous life is no protection against premature aging. Hollywood has produced numerous deplorable human beings who appear to languish in perpetual youth. It doesn't seem fair. Why do some people age prematurely while others, no matter how old they may be, always seem to look good for their age? Before answering this provocative question, I would like to propose a modest definition of premature aging.

#### DEFINITION

Premature aging can be defined as those changes of the body that when taken as a whole would make you feel self-conscious. Picture this scenario. You find yourself single and looking in the mirror before going out on a date with an old friend. You have not seen him, or her, in 40 years and, like you, he (or she) widowed. This person

has been thinking of you nonstop for the past three weeks since finding out that you are available again. In anticipation of your time together, your friend has been looking at old photographs of you which your younger sister so helpfully sent him. The pictures were taken at Bear Lake that magical summer so long ago. Back then, a bathing suit was something that served its principal purpose when worn with a deep dark tan. The tan, you now realize has contributed to the premature aging you are bearing witness to in the mirror as you prepare to face yet one more character-building experience. Since youth does such a poor job of preparing us for old age, it is safe to assume that, by my definition, practically everyone is aging prematurely.

#### CAUSE AND EFFECT

Until recently, patients seeking a more youthful appearance could either use makeup or undergo cosmetic surgery. Today, there are many rejuvenation treatments available for aging skin that do much more than camouflage and stretch. This article outlines the changes characteristic of aging skin, and new treatments that can turn the clock back for your patients, by creating healthier and younger looking skin.

Sagging, sinking, wrinkling and thinning of the skin, and subcutaneous fat and bone, all result from genetically driven, intrinsic aging of the skin. In other words, we are all in the same boat. However, for some the boat seems to be sinking faster. On a microscopic level, skin, fat and muscle cells are lost over time, as well as the cells that produce elastic and collagen fibers, which support the skin.

In addition to genetic influences, environmental factors play an important role in the aging of the skin. Tobacco smoke, alcohol consumption, and poor diet, are all contributors. But the principle catalyst to premature aging is the sun.

The sun produces energy from thermonuclear reactions in the core, where temperatures reach 25 million degrees. Charged particles called “solar wind” stream from the surface of the sun. The “solar wind” moves into space in the form of ultraviolet radiation. This radiation moves at a speed of a million miles an hour, not nearly fast enough for the average teenager lying impatiently by the pool with the belief that the main purpose of solar radiation is to assist her in her pursuit of a deep tan.

Blotching, thickening, roughness, thinning and dry-

ness are all due to overexposure to the sun, as are a variety of warty growths and cancers, the appearance of tiny blood vessels, bruising, and a general laxness of the skin. Along with the visible changes in the skin caused by sunlight, there are cellular changes, which contribute to an impaired immune response and increased susceptibility to disease.

Photo aging results from the cumulative effects of sun exposure and is more severe in light skinned people who spend excessive time outdoors. One over-tanned gardener described herself as “more handbag than housewife.” Alas, it’s never too late to start taking better care of oneself. Prevention is the first step in a good skin care program.

In fairness to the Gucci-gardener, when she was a girl a tan signified robust health and the knowledge of the damaging effects of the sun was generally unknown. The term “healthy tan” still enjoys common usage today, though most people know that overexposure to the sun causes cancer and photo aging of the skin. Staying out of the sun will eliminate the major source of non-genetic aging of the skin. However, completely avoiding the sun is impractical and undesirable. Some sun exposure is necessary for good health, but where do you draw the line?

“How much sun is too much?” There is no correct answer. Sun tolerance varies from person to person. What most experts do agree on is that sunburn is harmful, deep tanning is unwise, and the best way to enjoy the outdoors is to do so properly dressed and protected by an appropriate sun screen, during times of the day when the sun is lower in the sky.

“But, doctor, when I lay out I always use sun block.” Many people use sunscreens to increase their sun exposure rather than to decrease it, offering compelling evidence that our public education efforts have failed. Until lily-white skin is again in style, sunscreens will be the equivalent of not inhaling!

Most dermatologists recommend sunscreens with SPF’s of 30 that block both UV-A and UV-B. Repeated applications may be necessary since all available sunscreens wear off, sometimes surprisingly quickly when swimming or

working out. No sunscreen will reverse the signs of aging skin, but the proper use of sunscreens will help prevent further damage.

### TOPICAL TREATMENTS

Topical tretinoin (Retin A, Renova) was the first prescription drug with the ability to rejuvenate the skin. Tretinoin is a hormone that, when used persistently, increases dermal collagen and mucin, and decreases abnormal elastin and melanin. As a result of these cellular changes, the skin is smoother, less mottled, stronger, and has a rosy glow. Tretinoin, however, causes irritating rashes in many people, and increases sun sensitivity. Using a product with a lower concentration of tretinoin or using the product less frequently can prevent rashes. Vitamin E also reduces irritation from tretinoin in doses of 400 to 800 IU’s daily. Another drawback of tretinoin is that visible results may take many months.

### ALPHA HYDROXY ACIDS

Alpha hydroxy acids, AHAs (lactic, glycolic, or citric), which are found in hundreds of cosmetics, improve the color and texture of sun-damaged skin.

By law, the concentration of AHAs in cosmetics cannot exceed 10%. Physicians, on the other hand, may perform peels

using AHAs in concentrations up to 70%.

Though the exact mechanism of AHA’s action is not known, they can significantly improve the health and appearance of photo-damaged skin. A combination of Tretinoin and AHAs may produce superior results than when either is used alone. Unfortunately, AHAs work slowly, sometimes cause skin irritation, and are more effective for skin discolorations than wrinkles.

### VITAMINS

Both Vitamin C and E have beneficial effects on the health of the skin primarily through their antioxidant and anti-inflammatory properties.

Several studies have shown that Vitamins C and E aid in regenerating damaged tissues when taken orally or

MOST DERMATOLOGISTS RECOMMEND  
SUNSCREENS WITH SPFs OF 30 THAT  
BLOCK BOTH UV-A AND UV-B.  
REPEATED APPLICATIONS MAY BE  
NECESSARY SINCE ALL AVAILABLE  
SUNSCREENS WEAR OFF, SOMETIMES  
SURPRISINGLY QUICKLY WHEN  
SWIMMING OR WORKING OUT.

applied to the skin. However, few experts believe that vitamins, even in high doses, significantly reduce the visible signs of aging skin.

### HORMONES

Thinning skin caused by a loss of collagen and water is also characteristic of aging. Both oral estradiol and testosterone retard the loss of collagen and water from the skin resulting in a reduction in wrinkles. Topical and oral progesterone also have beneficial effects on aging skin including firming, moisturizing, smoothing, and improving color. With the exception of topical progesterone, which is thought to be very safe, a physician with expertise in endocrinology should monitor hormone therapy. The most popular progesterone formulation contains 10% progesterone in a pH neutral cream base that is applied to the skin twice daily. The most common untoward reaction to topical progesterone is disruption of the menstrual pattern. Reputed benefits include improvement in symptoms of fibrocystic breast diseases and a reduction of symptoms of the so-called Premenstrual Syndrome.

### TOPICAL 5-FLUOROURACIL

Skin cells which have been severely damaged by the sun require more DNA than normal cells. Fluorouracil (5-FU), a chemotherapeutic skin cream, preferentially interferes with DNA synthesis in pre-cancerous and cancerous cells. In many cases, 5-FU is preferable to surgery for the treatment of skin cancer, especially when the cancer is large but still shallow. The results of 5-FU are impressive, but the treatment is uncomfortable and the skin on patients' faces becomes swollen and scabby. Once the skin heals, however, it looks younger and feels firmer.

### SURGICAL RESURFACING

Resurfacing refers to the destruction of photo-damaged skin and the subsequent regrowth of healthier new skin. The wounding of the skin can be done either by a chemical, laser, or physical abrasion of the skin.

The two most common chemicals used for peels are trichloroacetic acid and phenol. Only experienced clinicians should perform peels with these chemicals because,

though the results can be dramatic, so can the complications. Disfiguring scarring, infection, and, when phenol is used, cardiac death are all possible consequences. The depth of the chemical injury is determined by the strength of the concentration of chemical used. Knowing the strength of the dilution and the duration of treatment requires a lot of experience and good judgment. The less experienced physician can use a product called AcuPeel, which is quite easy to use. It comes in a 100-gram tube containing 35% trichloroacetic acid cream, which is spread onto the face, left for 5 minutes, and then wiped off.

The skin will be red, and within minutes it begins to swell. In a day or two scabs appear, and in a week the scabs come off and the skin looks and feels better.

Lasers can also be used to destroy aged skin. Some investigators claim that the results from lasers thermal burns are superior to the chemical burns from peels, and others claim just the opposite. Many dermatologists and cosmetic surgeons use both modalities in their practices. It should be

noted that both treatments can be painful, expensive, and may require weeks or longer for complete recovery.

Dr. Mark Taylor, a dermatologist and cosmetic surgeon experienced in rejuvenating techniques, believes that when done properly, laser resurfacing produces better results than plastic surgery, with fewer risks and side effects.

Microdermabrasion entails sandblasting the skin with a special machine using aluminum oxide crystals or salt. The machine vacuums as it propels the abrasives, so there is little or no mess. A treatment takes about 30 minutes and is only slightly uncomfortable. Each successive treatment (usually a week or two apart) goes a little deeper into the skin, until the aged outer layers of the epidermis are stripped away, and new collagen stimulated. Microdermabrasion treatments can be repeated at any time, and the risk of complications is minimal. Microdermabrasion should not be performed on patients who are taking Accutane, using Retin A, or using Renova creams since unwanted pigment changes can occur in skin recently treated with these drugs.

Microdermabrasion has received considerable attention in the press, in popular magazines, and on televi-

WHILE MICRODERMABRASION HAS RECEIVED CONSIDERABLE ATTENTION IN THE PRESS AND IN POPULAR MAGAZINES AND TV SHOWS, MORE RESEARCH IS NEEDED TO SUBSTANTIATE LONG-TERM RESULTS.



THESE “BEFORE AND AFTER” PHOTOGRAPHS ILLUSTRATE THE RESULTS OF LASER RESURFACING TREATMENTS.

Photo credits: Grant R. Fairbanks, M.D.

sion magazine programs, which often give glowing reports about immediately eliminating or reducing lines, enlarged pores, small veins, and unsightly blotches. Even some well known medical journals have published reports from researchers who claim that microdermabrasion works as advertised. While much of this may be so, and most patients who undergo microdermabrasion seem to be pleased, more research is needed to substantiate long-term results. Discomfort, infection, bruising, and scarring are among the rare complaints from patients who have undergone microdermabrasion.

Old-fashioned wire-brush dermabrasion machines are difficult to control and pose a hazard to the doctor and his staff as blood is sprayed into the air.

Another strategy for reducing wrinkling is autologous fat transfers. In this procedure fat is usually taken from the abdomen, buttock or thighs by syringe and re-injected into facial wrinkles. In the hands of a skilled surgeon, fat grafting is an excellent approach to deep lines and furrows since it is safe and relatively painless. The drawback to autologous fat transfers is that not all of the deployed fat survives, and sometimes none of it does. The skill of the surgeon is crucial to success in fat grafting.

Various biologic, synthetic and semi-synthetic materials may be injected or inserted into the skin to reduce wrinkles and depressions. These materials, including botulinum toxin and bovine collagen are expensive, and though they reduce wrinkling, they do nothing to improve the health of the skin. Moreover, the injectable products are temporary, with results often disappearing in a few short months.

Arguably, of all the treatments now available for aging skin, cosmetic surgery produces the most dramatic results. What is not disputed, however, is that surgery does nothing to rejuvenate the skin. In fact, there is mounting evidence that pulling the skin taut tears the elastic fibers and collagen bundles that are already unhealthy, ultimately resulting in more sagging and wrinkling. This is not to discount face-lifts, but more and more plastic surgeons are using new skin rejuvenation techniques to augment their surgical procedures to get the most long-lasting results.

#### SUMMARY

Aging skin is an inevitable indignity we all suffer. The furrows, stains, and droops are on display for everyone to see. Until recently, all that medical science had to offer for aging skin was smoke and mirrors. Today, however, there are real treatments for old skin, which not only improve appearance, but also actually make the skin healthier and less prone to disease and injury.

Growing old gracefully, at least as far as the skin is concerned, is now easier with new products and procedures. If one of these approaches is to be taken, referral should be made to a physician who has considerable experience. If possible, you may also want to interview previous patients who have undergone the treatment you are considering.

And above all, wear your sunscreen.

---

*Richard W. Parkinson, M.D. is a practicing dermatologist in Orem, Utah.*





