The Eleventh International Conference on

Health Problems Related to the Chinese American In North America

Proceedings

2002

Roosevelt Hotel
New York, NY

The Eleventh International Conference on

HEALTH PROBLEMS RELATED TO THE CHINESE IN NORTH AMERICA

May 25-26, 2002
The Roosevelt Hotel
New York, NY

Proceedings

Edited by

Hsueh hwa Wang, M.D.

The Conference is hosted by:

The Chinese American Medical Society,
The Charles B. Wang Community Health Center, *and*
Chinese American Independent Practice Association

The Scientific Program is sponsored by:

The NYU Downtown Hospital

ACCREDITATION

The NYU Downtown Hospital is accredited by the Medical Society of the State of New York (MSSNY) to sponsor continuing medical education for physicians. The NYU Downtown Hospital accredits this Scientific Program, exclusive of poster exhibits and luncheon presentations, for 9.5 credits in Category I Continuing Medical Education, as applied toward the AMA Physician's Recognition Award.

The Eleventh International Conference on

HEALTH PROBLEMS RELATED TO THE CHINESE IN NORTH AMERICA

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The Chinese American Medical Society,
The Charles B. Wang Community Health Center, *and*
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An Activity of
The Federation of Chinese American and Chinese Canadian Medical Societies

Association of Chinese Canadian Professionals, Vancouver, BC, Canada
Association of Chinese Community Physicians, San Francisco, CA
Chinese American Medical Association of Southern California, Los Angeles, CA
Chinese American Medical Society, New York, NY
Chinese American Physicians Society, East Bay, Oakland, CA
Chinese Canadian Medical Society, Ontario, Canada
Chinese American Health Care Association, San Francisco, CA
Chinese Hospital Medical Staff, San Francisco, CA
Philippine Chinese American Medical Association, New York, NY

CONFERENCE HISTORY

This Conference was founded in 1982 by the Chinese Hospital Medical Staff in San Francisco. The conference brought together a number of Chinese American and Chinese Canadian medical societies, as well as many North American and international physicians interested in health problems of the Chinese in North America. A steering Committee was formed to oversee the continuing development of the Conference on a biennial basis. In 1994, the Federation of Chinese American and Chinese Canadian Medical Societies in North America (FCMA) was founded. Subsequently, the Conference is the activity of FCMS.

CONFERENCE OBJECTIVES

1. to congregate physicians and scholars to discuss health and health related problems in the Chinese in North America.
2. to establish a database of disease patterns in this population.
3. to establish comparative data on health problems related to cultural assimilation.
4. to encourage clinical and/or basic research in health problems affecting the Chinese in North America.
5. to publish proceedings of the Conference as a means of expanding access to resources on these health problems

PREVIOUS CONFERENCES

May 22-23, 1982	San Francisco
August 18-19, 1984	Los Angeles
August 23-24, 1986	New York City
April 22-23, 1988	San Francisco
April 23-24, 1990	Toronto
June 18-21, 1992	San Francisco
July 1-3, 1994	New York City
August 22-25, 1996	Vancouver
August 21-23, 1998	Los Angeles
June 30-July 1, 2000	San Francisco

NEXT CONFERENCE

YEAR 2004	Vancouver

Outstanding Achievement Awards

The Outstanding Achievement Award is presented by the Federation of Chinese American and Chinese Canadian Medical Society to persons who have contributed extraordinarily to the growth and ongoing success of the International Conference on Health Problems Related to the Chinese in North America.

Previous recipients of the Outstanding Achievement Award have been:

Kenneth D. Chan, M.D., San Francisco
Huo Chen, M.D., Los Angeles
Lillian Chen, M.D., New York City
David T. W. Chiu, M.D., New York City
John H. C. Chiu, M.D., North York, Ontario
Edward Chow, M.D., San Francisco
Gordon L. Fung, M.D., San Francisco
Gregory Fung, M.D., San Francisco
Harry Lee, M.D., San Francisco
Stuart Quan, M.D., New York City
Collin P. Quock, M.D., San Francisco
Hsueh-hwa Wang, M.D., New York City

ACKNOWLEDGEMENTS

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We express our deep gratitude to all the Conference members, CAMS Board members and many volunteers who spent numerous hours in the planning of the Conference, with special thanks to Peggy Sheng and Susan Lau

THE CITY OF NEW YORK
OFFICE OF THE MAYOR
NEW YORK, N.Y. 10007

May 25, 2002

Dear Friends:

I am delighted to welcome everyone attending the Eleventh Conference on Health Problems Related to the Chinese in North America.

This is an important event for the healthcare and well being of Chinese Americans. In the aftermath of 9/11, Chinatown suffered greatly, not only economically and socially but also in the physical and emotional health of its residents and workers. Its proximity to Ground Zero amplifies the issues Chinatown now faces.

The Conference on Health Problems Related to the Chinese in North America brings together physicians and participants from a variety of hospitals and organizations in an effort to deal with the issues facing this community.

I am grateful to the Chinese American Medical Society, the Chinatown Health Clinic of New York City and the NYU Downtown Hospital for hosting this event. On behalf of our City, I offer my best wishes for an informative and enjoyable conference.

Sincerely,

Michael R. Bloomberg

Michael R. Bloomberg
Mayor

NEW YORK STATE ASSEMBLY

May 25, 2002

Dear Friends:

Please accept my sincerest greetings as you gather for *The Eleventh Conference on Health Problems Related to the Chinese in North America*.

As the Chinatown Community tries to cope with the aftermath of the World Trade Center disaster, which has had a severe impact on the physical, psychological and emotional health of all community members, this weekend's conference is an important step in the community's healing process. With topics ranging from community health updates to in-depth discussions of stroke, hepatitis, diabetes, cardiovascular disease, mental health problems, renal disease, gene therapy, complementary medicine and organ transplant surgery, this conference will provide for a serious discussion of the health problems affecting the Chinese Community in New York City and beyond. The Chinese American Medical Society, the Chinatown Health Clinic of New York City, and NYU Downtown Hospital should be proud of their efforts to organize such an important conference, and I salute these organizations for a job well done.

Again, welcome to the conference, and best wishes for a productive conference and continued success.

Sincerely,

SHELDON SILVER
Speaker

NEW YORK CITY HEALTH AND HOSPITALS CORPORATION
125 Worth Street • New York • New York • 10013
212-295-5810 Fax: 212-295-5645 E-mail: CHUBMD@NYCHHC.ORG

Benjamin K. Chu, M.D.
President

Dear Colleagues:

As President of the New York City Health and Hospitals Corporation (HHC), I would like to extend my support for the Eleventh Conference on Health Problems Related to the Chinese in North America. This conference, co-sponsored by the Chinese American Medical Society and Chinatown Health Clinic, New York, NY, brings Chinese physicians and scholars together to discuss health and health related problems impacting the Chinese community. The conference will assist HHC improve its provision of health care to ten percent of our patient population.

As you know, the Institute of Medicine report finds that minorities receive inferior health care and that this racial and ethnic disparity exists regardless of income or insurance coverage. In addition, immigrant communities face other barriers to care such as limited English proficiency and a lack of cultural competency in many institutions. HHC is committed to providing the highest level of care for our patients, and that each person is treated with dignity and respect, cultural sensitivity and compassion regardless of ability to pay. In fact, the care HHC provides to minority communities equal or surpass the nationally reported care provided to the non-minority white population.

While HHC is doing better than the nation as a whole in the provision of health care to minority communities, there is a lot more that could be done to decrease disparity between minority and whites as it relates to morbidity and mortality. Events like the Eleventh Conference on Health Problems Related to Chinese in North America looks at disease patterns and comparative health data for Chinese patients, in addition to encouraging clinical and basic research by Chinese physicians and scholars. HHC hopes to benefit from such collaborations to improve health outcomes for our Chinese patients.

Sincerely,

Benjamin Chu, M.D., MPH

OFFICE OF THE COMMISSIONER
HONG KONG
ECONOMIC AND TRADE AFFAIRS, USA
1520 18th Street, N.W., Washington, D.C. 20036-1306

香港駐美國
總經濟貿易專員

May 2002

I am delighted to extend my best wishes to the Chinese American Medical Society on the occasion of its Eleventh Health Conference on Health Problems Related to the Chinese in North America.

Advances and breakthroughs in molecular and genomic technologies are opening up new horizons for the diagnosis and the treatment of diseases, which will enable us to live longer and enjoy a better quality of life. Hong Kong is well positioned to become a leader in the niche area of bio-medical research and the development of treatment of diseases that are unique to or common among Chinese and Asian people.

As the Hong Kong Special Administrative Region's Commissioner to the United States, I am pleased to see the Chinese American Medical Society addressing the important issue of health problems of Chinese communities in North America. I am particularly pleased to note that this International Conference includes participants from Hong Kong. This is yet another demonstration of the strong social and economic ties between the United States and Hong Kong.

I wish you all every success in the Conference.

Jacqueline Willis

Miss Jacqueline A. Willis
Hong Kong Commissioner, USA

Telephone (202) 238-6336 • Facsimile (202) 331-8958 • E-mail jacqueline_willis@hketowashington.gov.hk

NYU Medical Center
NYU DOWNTOWN HOSPITAL

LEONARD A. AUBREY
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February 1, 2002

Daisy Saw, M.D., Co-Chair
John Wang, M.D., Co-Chair
Chinese American Medical Society
281 Edgewood Avenue
Teaneck, NJ 07666

Dear Drs. Saw and Wang:

On behalf of the Trustees, physicians and staff of NYU Downtown Hospital, I want to welcome you to New York City for your eleventh Conference on Health Problems Related to the Chinese in North America. I want to thank you for choosing our great city to hold this important conference for members of the Chinese medical community. I also want to thank the Chinatown Health Clinic, our partners in serving the local Chinese community, for joining the Chinese American Medical Society in sponsoring the Conference.

As you probably know, NYU Downtown Hospital is the leading healthcare provider for the Chinese community in New York City. Many of the leading members of CAMS practice medicine at our Hospital. We are extremely proud of the contributions all of our Chinese physicians make to community and, equally important, proud of their research on health problems and their strong advocacy for improving the health of New York City residents of Chinese heritage.

I hope you have a successful and productive Conference, and an enjoyable weekend in New York City. You and your colleagues should always feel free to call on NYU Downtown Hospital for any assistance you may need.

Sincerely,

Leonard Aubrey

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FEDERATION OF CHINESE AMERICAN AND CHINESE CANADIAN MEDICAL SOCIETIES

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Website: http://www.fcmsdocs.org

Dear Participant:

Thank you for coming, and welcome to the Big Apple! As the retiring Board Chairman of the Federation of Chinese American and Chinese Canadian Medical Societies, I wish you a wonderful time updating your medical knowledge while you enjoy the camaraderie so unique to this Conference. We merge the latest currents in modern medicine with the sensitivities and outlook of our Chinese heritage against a North American backdrop.

I apologize for my absence as our son is graduating from his MBA program in San Francisco, and I must leave immediately after the Board meeting on Friday. It is the first time I shall miss this Conference since its birth in 1982.

My term as Chairman comes to an end with a hunger of wishing I could have done more, but the leadership of the FCMS is in excellent hands with Drs. Hsueh-hwa Wang and Caroline Wang. I do thank the Board members and committee chairs for their hard work and marvelous achievements since the Tenth Conference in San Francisco two years ago.

We have had an eventful administration. I am pleased to announce that last month, the FCMS Foundation was officially licensed in California. They can now go about raising funds to support the mission of the Federation. I am grateful for the rebirth of our website, the launching of our newsletters, and the start of an organized research program, including three new research initiatives. The International Office has been moved to a larger suite in Chinese Hospital, San Francisco. We have installed new office furnishings, including computers. A fund development program has been started and a search is underway for staffing. Fresh organizational starts have been made in Los Angeles, Seattle, and Calgary; and the stage is now set for an aggressive recruitment of individual members. Ties to our Toronto friends were strengthened by a busy board meeting there.

All of this progress has been made by a volunteer staff and a cadre of volunteer physicians. We have come a long way in between Conferences, and I extend my deepest gratitude and that of the entire FCMS to Patricia Chung, CMSC, and her assistant, Ms. Isabella Lee, for their dedication and their excellent supportive skills. They have made the FCMS what it is today. I also wanted to congratulate Dr. Hsueh-hwa Wang and her New York associates for this fantastic Conference. It holds the promise of being the best ever, despite organizing problems imposed by tragic terrorist events this past year.

I wish the incoming officers the same marvelous experience I have enjoyed at the helm of the FCMS. God bless you all as you carry on the mission of the Federation.

Very sincerely yours,

Collin P. Quock, MD, FACP, FACC
Chairman, Board of Directors
June 2000 – May 2002

The Eleventh Conference on Health Problems Related to the Chinese in North America

co-sponsored by: ***Chinese American Medical Society*** *and* ***Chinatown Health Clinic, New York, NY***

An activity of The Federation of Chinese American and Chinese Canadian Medical Societies (FCMS)

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website: www.fcmsdocs.org

May 25, 2002

Dear Friends:

We are delighted to have the opportunity to co-chair the Eleventh International Conference on Health Problems Related to the Chinese in North America. It is our great pleasure to extend warmest greetings to all participants.

As President and Immediate Past President, respectively, of the Chinese American Medical Society (CAMS), we express our sincere appreciation to the Board of Directors for their active involvement in raising funds, organizing events, and coordinating an excellent scientific program. We wish to thank the Chinese American Independent Practice Association and the Charles B. Wang Community Health Center for co-hosting the Conference. We would like also to thank NYU Downtown Hospital to sponsor us for the CME credits, and all the vendors for their generous financial support of our activities.

The Federation of Chinese American and Chinese Canadian Medical Societies (FCMS) is to be commended for continuing this highly respected health education program for the Chinese in North America.

In 1994, New York was the host for the Seventh Conference and we are honored to be selected again. The events of September 11 have made it a priority to ensure that "the show must go on" in New York.

WELCOME TO NEW YORK!

Best Wishes,

Daisy Saw, M.D.
Co-Chairman

John C. L. Wang, M.D.
Co-Chairmen

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Scientific Program

*Sponsored by **NYU Downtown Hospital***

Frieday, May 24, 2002 (4 Pm to 6 PM) Reception (The Palm Room)

Saturday, May 25, 2002 (8:30 AM to 5 PM)

Morning: One session (Grand Ballroom)

8:30 AM Opening Remarks
Hsueh hwa Wang, M.D., President, FCMS
Daisy Saw, M.D. and John Wang, M.D., Conference Co-Chairmen

8:45 AM Keynote Speaker: (introduced by Daisy Saw, M.D.)
David Ho, M.D. "HIV pathogenesis and implications for Therapy"

Symposium on Common Medical Diseases (Part I)
Modrators: Tak Kwan, M.D. and George Liu, M.D.

9:30 AM Statins: Are There Benefits Beyond Cholesterol Lowering?
James Liao, M.D

10:15 AM Asians, Insulin Resistance, and PPAR Gamma. *Willa Hsueh, M.D.* (sponsored by GlaxoSmithKline Pharmaceutical Company)

11:00 AM Update on Viral Hepatitis. *Danny Chu, M.D.*

11:45 AM to 12: 15 PM Poster Presentation: (Promenade)

12:15 PM Lunch (Terrace room)
Luncheon Speaker: (introduced by Tak Kwan, M.D.)
Benjamin Chu, M.D./MPH:" Health Care Directions for the Public Hospitals and the City of New York"

Afternoon: Two concurrent sessions

Symposium on Common Medical Diseases (Part II) (Grand Ballroom)
Moderators: John Wang, M.D. and Chun K. Yip, M.D.

2:00 PM Treatment of Diabetic Macular Edema. *Stanley Chang, M.D*

2:45 PM State of the Art: Congenital Heart Disease 2002. *Daphne Hsu, M.D*

3:30 PM Fabry's Disease: From Molecular Diagnosis to Enzyme Therapy .
Y. Howard Lien, M.D.,

4:15 PM COPD: State of the Art. *Chun K. Yip, M.D*

Symposium on Innovative Therapy (Plaza Suite)
Moderators: Wilson Ko, M.D. and Pak Chung, M.D.

2:00 PM Ventricular Assist Devices and the Total Artificial Heart: The Bionic Man Revisited.
Benjamin Sun, M.D.

2:45 PM Regenerative Biology and Medicine: A Science Whose Time Has Come.
Ray C. J. Chiu, M.D./Ph.D.

3:30 PM Current Concepts in the Management of Colorectal Cancer.
W. Douglas Wong, M.D.,

4:15 PM Assisted Reproductive Technology. *Pak Chung, M.D.* (sponsored by the Ferring Pharmaceutical Company)

6:30 PM Banquet dinner at the University Club, 1 West 54th St, New York, NY

Sunday, May 26, 2002 (8:30 AM to 2 PM)

Morning (Grand Ball Room)

8:30 AM Keynote Speaker: (Introduced by John Wang, M.D.)
Savio Woo, Ph.D., "Gene therapy as Molecular Medicine in the 21st Century".

Two concurrent sessions:

Symposium on Alternative Medicine (Grand Ballroom)
Moderators: Victor Chang, M.D. and David Zhang, M.D.

9:30 AM NCCAM Perspectives on Research on Complementary and Alternative Medicine: Past, Present and Future. *Shan S. Wong, Ph.D.*
10:15 AM Commonly Used Natural Products, What is safe? *David Zhang, M.D*
11:00 AM The Brown Paper Bag Problem and Traditional Chinese Medicine. *Elaine Kang-Yum, R.Ph..*
11:45 AM Is Acupuncture Effective for the Treatment of Chronic Pain? An Objective Assessment. *Bryan O'Young, M.D.*

Symposium on Neurology and Psychiatry (Plaza Suite)
Moderators: Henry Chung, M.D. and Sun-Hoo Foo, M.D.

9:30 AM Stroke Among Chinese in New York City. *Sun-Hoo Foo, M.D*
10:15 AM Recent Advances in MRI Technology in the Diagnosis and Treatment of Ischemic Stroke. *Chung Y. Hsu, M.D./Ph.D.*
11:00 AM Cardiovascular Disease and Depression, Recognition and Treatment. *Henry Chung, M.D.* (employed by Pfizer, Inc.)
11:45 AM The Prevalence of Mental Health Problems Among Asian American Adolescents and Children: Symptoms and Treatment Issues. *Irene Chung, Ph.D.*
12:30 PM Lunch (Terrace Room)
Luncheon Speaker (introduced by Fun-Sen Yao, M.D.)
Henry Lee, Ph.D., "Signs and the Crime".

Educational Goal

This Conference is designed for the interest of primary care physicians, internists, surgeons, gynecologists, neurologists, and psychiatrists. Topics will deal with diseases often afflicting the Chinese in North America and information on new and innovative therapy will be presented. The common medical diseases covered include diabetes, vascular disease, hepatitis, congenital heart disease, renal disease and chronic obstructive pulmonary disease. Innovative therapies include the artificial heart, regenerative biology, treatment of colorectal cancer and assisted reproductive technology. A symposium on alternative medicine covers the current research and use of traditional Chinese medicine and the effectiveness of acupuncture. Last but not least, a symposium on neurology and psychiatry presents stroke, depression, and mental health problems among Asian adolescents and children.

HIV Pathogenesis and Implications for Therapy

David D. Ho, M.D.

It is safe to say that the global AIDS epidemic will get much worse before it gets any better. Sadly, this modern plague will be with us for several generations to come, despite the major scientific advances of the recent past and near future.

At the beginning of the new millennium, the AIDS epidemic had already claimed 22 million lives, while leaving 40 million persons living with a viral infection that slowly but relentlessly erodes the immune system. Accounting for over 3 million deaths in the year 2000 alone, the AIDS virus has become the most deadly microbe in the world, exceeding even TB and malaria. There are now 34 developing countries wherein the prevalence of this infection is 2% or greater. In Africa, nearly a dozen countries have an infection rate higher than 10%, including 4 southern nations where a quarter of their citizens are already infected. And the situation continues to worsen, with over 5 million new infections worldwide in 2000. This number is figuratively akin to sentencing 16,000 people each day to a slow and miserable death.

Fortunately, the AIDS story has not been all gloom and doom. Within two years of recognizing AIDS as a new syndrome in 1981, the causative agent—now called human immunodeficiency virus or HIV—was identified. Shortly thereafter a blood test became widely available in developed countries, along with the first effective drug, AZT. The scientific community now knows more about HIV than any other virus, and 15 AIDS drugs have been developed and licensed in the United States and Western Europe. The effective use of some of these drugs in combination has resulted in unprecedented control of HIV replication in many infected patients, resulting in restoration of the immune system and dramatic declines in AIDS deaths in the better developed countries.

But as we look ahead, AIDS will become even more devastating to Sub-Saharan Africa, particularly in the south. It will be by far the major killer of young Africans; decreasing life expectancy to as low as 40 years in some countries and single-handedly erasing the public health gains of the past 5 decades. In addition to the massive human toll, the epidemic will threaten the socioeconomic and political fabric of numerous nations on the continent. The growth of the epidemic in South America and Eastern Europe will remain severe. The global picture of AIDS, however, will be influenced most by developments in Asia because of its huge population at risk. The magnitude of the pandemic will be influenced greatly by what happens in India and China. India already has 3-4 million infected persons, but the prevalence of infection is likely to reach a few percent in a population of 1 billion. Over 850,000 Chinese are now infected, but the trajectory of its epidemic in the coming decades, although worrisome, is less certain.

An explosive AIDS epidemic in the United States is unlikely. Instead, HIV infection will continue to fester at a level of about 0.5% of the population, but the complexion of the epidemic will change greatly though. New HIV infections will occur predominantly in the underclass, with rates being 10 times higher in minority groups. Nevertheless, American patients will live quality lives for decades, thanks to advances made in medical research. Dozens of powerful and well-tolerated AIDS drugs will be developed, as will novel means to aid the restoration of the immune system. A cure for

AIDS in the long run is not inconceivable. But constrained by economic reality, these therapeutic advances will only have limited benefit in regions beyond the U.S. and Western Europe.

The development of a vaccine to block the continued spread of HIV is our only real hope to avert a global disaster unparalleled in medical history. A concerted effort in vaccine research in the U.S. was launched several years ago under a presidential directive. Hints of promising vaccine strategies are already emerging from recent experiments in monkeys. There is renewed confidence that the talent and creativity of biomedical scientists will produce a protective AIDS vaccine in the coming years. But the eventual elimination of AIDS will also require the political will of our world leaders to acknowledge the enormity of this human crisis and to make the necessary commitment of resources.

David D. Ho, M.D. is Director and CEO, Aaron Diamond AIDS Research Center and Irene Diamond Professor, The Rockefeller University

Gene Therapy as Molecular Medicine in The 21st Century

Savio L.C. Woo, Ph.D.

Gene therapy is the use of genes as medicines for the purposes of preventing the occurrence of disease or for altering the clinical course of an existing disease. Over the past decade, dramatic progress has been made by many investigators in the field to develop and refine technologies used to deliver genes into various cells and organs in living animals, including humans. In several instances, significant treatment benefits achieved in laboratory animal models of human disease have been observed in recent clinical studies as well. An example is Hemophilia B, which is caused by a deficiency of clotting factor IX in the blood. Normal blood clotting times have been restored for extended durations of time after a single application of the gene in genetically affected mice and dogs. Very encouraging results have also been reported in patients during early phase clinical studies after intramuscular de-livery of a recombinant adeno-associated virus expressing the human factor IX gene. Another example is X-Linked Severe Combined Immunodeficiency Syndrome secondary to a deficiency of the gamma chain of cytokine receptors on T cells. Autologous transplantation of CD34+ cells transduced with a recombinant retroviral vector expressing the normal human gene has resulted in the reconstitution of T cell counts and immune functions in several affected children for up to one year. These achievements resulted from recent technological advancements and will lead not only to extensive applications in the treatment of patients affected with relatively rare inherited disorder such as Phenylketonuria (PKU), but also to the future treatment of complex and acquired disorders such as cardiovascular diseases, cancers, diabetes, obesity, infectious diseases and neurodegenerative dis-orders that represent the leading causes of mortality and morbidity in developed countries.

The most notable recent accomplishments in these areas include, but are not limited to, the treatment of patients with ischemic limbs by the administration of an angiogenic gene that stimulates blood vessel growth, and the destruction of tumors in patients by the administration of suicide and immunomodulatory genes that specifically destroy cancer cells. While the gene treatments for these complex disease targets are only partially effective at present, future advancements in technologies for the delivery of novel genetic medicines promise to result in much improved clinical benefits for these and other human diseases. It is anticipated that the scientific principles of gene therapy as a new biomedical discipline will be further validated in the coming years and decades. Its future widespread applications in the treatment of various human diseases will have a major impact on the practice of medicine, health and healthcare delivery in this Century.

(Savio Woo. Ph.D. is Professor and Director, Institute for Gene Therapy and Molecular Medicine, Mt. Sinai School of Medicine)

Statins:

Are There Benefits Beyond Cholesterol Lowering?

James K. Liao, M.D.

Objectives:

At the end of this presentation, the participant will be able to:

1. Appreciate the non-cholesterol effects of statins
2. Understand the role of nitric oxide in cardiovascular disease
3. Understand the mechanism by which statins protect against stroke

Summary:

The 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors, or statins, are potent inhibitors of cholesterol synthesis and large clinical trials have demonstrated that these agents reduce cholesterol and the incidence of cardiovascular diseases. Recent evidence, however, suggests that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels. Because statins also inhibit the synthesis of isoprenoid intermediates in the cholesterol biosynthetic pathway, they may have pleiotropic effects on vascular wall cells. In particular, the small GTP-binding protein, Rho, whose membrane localization and activity are affected by post-translational isoprenylation, may play an important role in mediating the direct vascular effects of statins.

Recent large clinical trials have demonstrated that a class of cholesterol-lowering agents called statins decrease the incidence of myocardial infarctions and ischemic strokes in hypercholesterolemic and atherosclerotic individuals (Scandinavian Simvastatin Study Group, 1994; Packard, 1998; Sacks et al., 1996). These agents inhibit an early step in cholesterol biosynthesis by blocking the conversion of HMG-CoA to mevalonate (Fig. 1). Because serum cholesterol level is strongly associated with coronary atherosclerotic disease (Klag et al., 1993), it has been generally assumed that cholesterol reduction by statins is the predominant, if not the only mechanism, underlying their beneficial effects in cardiovascular diseases. However, subgroup analyses of large clinical trials have challenged this notion and suggest that the beneficial effects of statins may extend to mechanisms beyond cholesterol reduction (Massy et al., 1996; Blum, 1994); possibly involving direct effects on the vascular wall.

For example, subgroup analysis of the WOSCOP and CARE trials indicate that despite comparable serum cholesterol levels, statin-treated individuals have significantly lower risks for coronary heart disease compared to age-matched placebo-controlled individuals (Shepherd et al., 1995; Sacks et al., 1996; Massy et al., 1996). Furthermore, meta-analyses of past clinical trials suggest that the risk of myocardial infarctions in individuals treated with statins is significantly lower compared to individuals treated with other cholesterol-lowering agents or modalities despite comparable reduction in serum cholesterol levels in both groups (Brown et al., 1993;

Pekkanen et al., 1990). Taken together, these findings suggest that some of the beneficial effects of statins may be due to their cholesterol-independent effects on vascular wall.

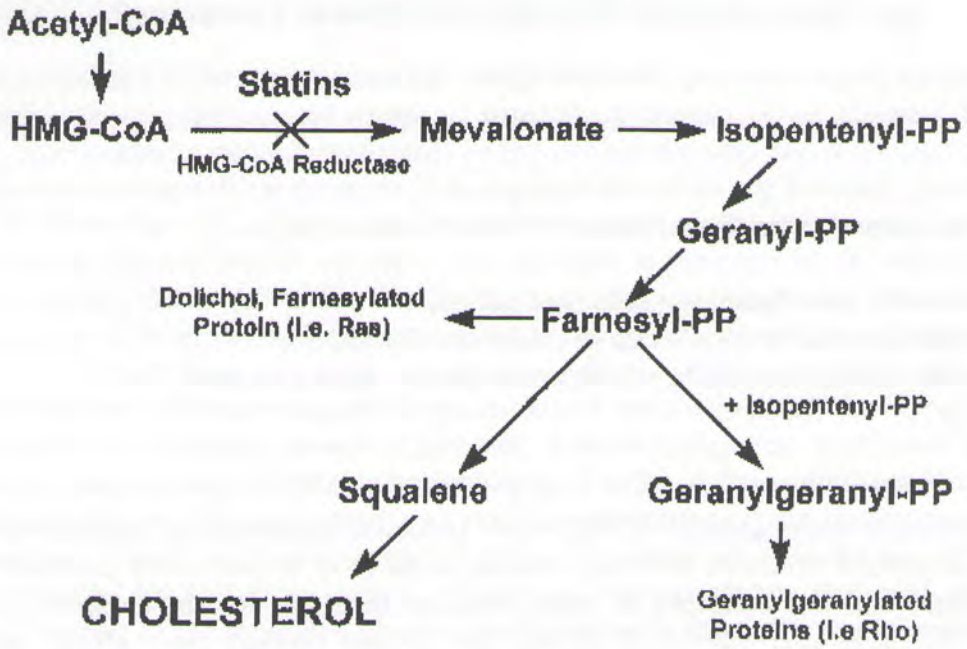

FIGURE 1 ; **Pathway for Cholesterol Biosynthesis.** Inhibition of HMG-CoA reductase by statins decreases the synthesis of isoprenoids and cholesterol.

Statins and Endothelial Function

Hypercholesterolemia impairs endothelial function and endothelial dysfunction is one of the earliest markers of arteriosclerosis, occurring even in the absence of angiographic evidence of disease (Liao, 1998; Libby et al., 1997). The vascular endothelium serves as an important autocrine/paracrine organ that regulates vascular wall contractile state and cellular composition. An important characteristic of endothelial dysfunction is the impaired synthesis, release and activity of endothelial-derived nitric oxide (NO). Endothelial NO has been shown to inhibit several components of the atherogenic process. For example, endothelium-derived NO mediates vascular relaxation and inhibits platelet aggregation, vascular smooth muscle proliferation and endothelial-leukocyte interactions. Furthermore, inactivation of NO by superoxide anion ($O_2 \cdot^-$) limits the bioavailability of NO and leads to nitrate tolerance, vasoconstriction, and hypertension (Harrison, 1997; Munzel et al., 1995).

Plasma LDL apheresis improves endothelium-dependent vasodilatation (Tamai et al., 1997) suggesting that statins could restore endothelial function by lowering serum cholesterol levels. However, in some studies, restoration of endothelial function occurs before significant reduction in serum cholesterol levels (Anderson et al., 1995; O'Driscoll et al., 1997; Treasure et al., 1995) suggesting that there are additional effects on endothelial function beyond that of cholesterol reduction. Indeed, statins upregulate endothelial nitric oxide synthase (eNOS) expression and activity and reverse the downregulation of eNOS expression by hypoxia and oxidized low-

density lipoprotein (ox-LDL) under cholesterol-clamped conditions (Laufs et al., 1997; Laufs et al., 1998a). Therefore, it is possible that statins may have other beneficial effects, irrespectively of serum cholesterol levels, in conditions associated with endothelial dysfunction such as atherosclerosis, pulmonary hypertension, and congestive heart failure.

It is also important to emphasize that commercially-available statins were initially selected on the basis of their predominant uptake by the liver since this is where greater than 65% of cholesterol biosynthesis takes place in the body. However, the effect of statins on eNOS expression is probably due to a direct non-cholesterol effect on vascular endothelial cells. This may be important when one considers that the statins differ with regard to their lipid solubility; and hence, their differential abilities to penetrate vascular wall cells. For example, the more lipid soluble statins such as simvastatin and lovastatin would be expected to penetrate endothelial cells more than that of the more hydrophilic statin, pravastatin.

Statins and eNOS

By inhibiting L-mevalonate synthesis, statins also prevent the synthesis of other important isoprenoid intermediates of the cholesterol biosynthetic pathway, such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) (Goldstein and Brown, 1990). These intermediates serve as important lipid attachments for the post-translational modification of variety of proteins, including the α subunit of heterotrimeric G-proteins, Heme-a, nuclear lamins, and small GTP-binding protein Ras, and Ras-like proteins, such as Rho, Rab, Rac, Ral or Rap (Van and D'Souza-Schorey, 1997). Thus, protein isoprenylation permits the covalent attachment, subcellular localization, and intracellular trafficking of membrane-associated proteins such as Rho. Members of the Ras and Rho GTPase family are major substrates for post-translational modification using isoprenoids (Van and D'Souza-Schorey, 1997; Aktories, 1997; Hall, 1998). Both Ras and Rho are small GTP-binding proteins which cycle between the inactive GDP-bound state and active GTP-bound state. In endothelial cells, Ras translocation from the cytoplasm to the plasma membrane is dependent upon farnesylation while Rho translocation is dependent upon geranylgeranylation (Laufs and Liao, 1998b). Statins inhibit both Ras and Rho isoprenylation and lead to accumulation of inactive Ras and Rho in the cytoplasm.

While the effects of statins on Ras and Rho isoprenylation are reversed in the presence of FPP and GGPP, respectively, the effects of statins on eNOS expression is only reversed with GGPP and not by FPP or LDL-cholesterol (Laufs and Liao, 1998b). These findings are consistent with a non-cholesterol-lowering effect of statins and suggest that inhibition of Rho by statins upregulate eNOS expression. Indeed, statins upregulate eNOS expression by prolonging eNOS mRNA half-life but not eNOS gene transcription. Since hypoxia, oxidized LDL, and cytokines such as TNF-α decrease eNOS expression by reducing eNOS mRNA stability, the ability of statins to prolong eNOS half-life may make them effective agents in counteracting conditions which downregulate eNOS expression. Statins prevent the downregulation of eNOS by oxidized LDL and TNF-α and under hypoxic conditions (Laufs et al., 1997; Laufs et al., 1998a).

Because Rho is major target of geranylgeranylation, inhibition of Rho and its downstream target, Rho kinase, is a likely mechanism by which statins upregulate eNOS expression (Fig. 2). The evidence that Rho negatively regulates eNOS expression comes from three sets of

experiments. First, direct inhibition of Rho by *Clostridium botulinum* C3 transferase increases eNOS expression independent of isoprenylation. The C3 transferase ADP-ribosylates asparagine-41 of Rho and renders it biologically inactive in the GDP-bound state (Aktories, 1997). Second, inhibition of Rho by overexpression of a dominant-negative RhoA mutant, N19RhoA, also increases eNOS expression. Finally, direct activation of Rho by *Escherichia coli* cytotoxic necrotizing factor (CNF)-1 leads to a decrease in eNOS expression (Aktories, 1997). These results, therefore, identify Rho as a negative regulator of eNOS expression.

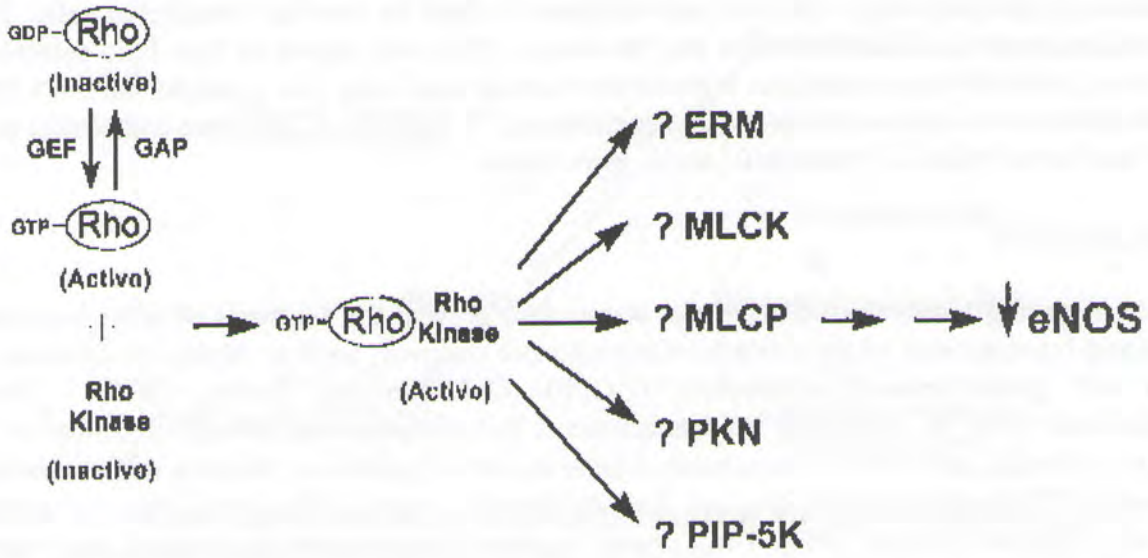

FIGURE 2: **Regulation of eNOS by Rho GTPase.** Rho activates Rho kinase which leads to the downregulation of endothelial nitric oxide synthase (eNOS). The downstream targets of Rho kinase include ezrin-moesin-radixin (ERM), myosin light chain kinase (MLCK), the myosin binding subunit of myosin light chain phosphatase (MLCP), protein kinase N (PKN), and phosphatidylinositol 5-kinase (PIP-5K).

Statins and Ischemic Stroke

An intriguing result of large clinical trials with statins is the reduction in ischemic stroke (Crouse et al., 1998). Although myocardial infarction is closely associated with serum cholesterol levels, neither the Framingham Study nor the Multiple Risk Factor Intervention Trial (MRFIT) demonstrated significant correlation between ischemic stroke and serum cholesterol levels (MRFIT Investigators, 1982; Sytkowski et al., 1990). Thus, the findings of these large statin trials raise the interesting question of how a class of cholesterol-lowering agents can reduce ischemic stroke when ischemic stroke is not related to cholesterol levels. It appears likely that there are pleiotropic effects of statins which are beneficial for ischemic stroke. Some of these beneficial effects may be attributed to the effects of statins on endothelial function and the vascular wall.

Cerebral vascular tone and blood flow are regulated by endothelium-derived NO (Dalkara et al., 1994). Mutant mice lacking eNOS (eNOS-/-) are relatively hypertensive and develop greater proliferative and inflammatory response to vascular injury (Huang et al., 1995). Indeed, eNOS-/- mice develop larger cerebral infarcts following cerebrovascular occlusion (Huang et al., 1996). Thus, the beneficial effects of statins in ischemic stroke may be due, in part, to their ability to upregulate eNOS expression and activity. Indeed, mice which were prophylactically treated with statins for up to 2 weeks, have 25-30% higher cerebral blood flow and 50% smaller cerebral infarct sizes following cerebrovascular occlusion (Endres et al., 1998; Laufs et al. 2000). Furthermore, no increase in cerebral blood flow or neuroprotection was observed in eNOS-/- mice treated with statins indicating that the upregulation of eNOS accounts for most, if not all, of the neuroprotective effects of these agents. Interestingly, treatment with statins did not affect blood pressure or heart rate before, during, or after cerebrovascular ischemia and did not alter serum cholesterol levels in mice, consistent with the previous finding that rodents are relatively resistant to changes in steady-state cholesterol levels by statins (Endres et al., 1998).

In addition to increases in cerebral blood flow, other beneficial effects of statins are likely to occur. For example, Lefer *et al.* reported that statins attenuate P-selectin expression and leukocyte adhesion via increases in NO production in a model of cardiac ischemia and reperfusion (Lefer et al., 1999). Others have reported that statins upregulate tissue-type plasminogen activator (t-PA) and downregulate plasminogen activator inhibitor (PAI)-1 expression through a similar mechanism involving inhibition of Rho geranylgeranylation (Essig et al., 1998). Thus, the absence of neuroprotection in eNOS-deficient mice emphasize the importance of endothelium-derived NO in not only augmenting cerebral blood flow, but also, potentially, in limiting the impact of platelet and white blood cell accumulation on tissue viability following ischemia. We speculate that statins may have contributed to the decrease in the incidence of ischemic strokes in clinical trials, in part, by reducing cerebral infarcts size to levels which are clinically unappreciated. Furthermore, because statins increase cerebral blood flow, these agents may also serve as an useful adjunctive therapeutic modality for increasing the delivery of other co-administered drugs to the CNS.

Summary

Statins exert many pleiotropic effects in addition to the lowering of serum cholesterol levels. Most of these effects are mediated by statin's inhibitory effect on isoprenoid synthesis. In particular, inhibition of Rho in vascular wall cells by statins leads to increased expression of atheroprotective genes and inhibition of vascular smooth muscle cell proliferation (Fig. 3). Thus, targeting Rho may have therapeutic benefits in the treatment of cardiovascular diseases.

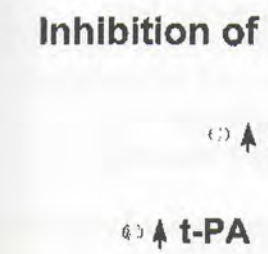

FIGURE 3: **Non-cholesterol Effects of Statins.** Inhibition of Rho in endothelial cells lead to the upregulation of nitric oxide (NO) and tissue-type plasminogen activator (t-PA), and downregulation of plasminogen activator inhibitor (PAI)-1.

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Asians, Insulin Resistance, and PPAR Gamma

Willa A. Hsueh, M.D.

Cellular proliferation and migration are fundamental processes that contribute to the injury response in major blood vessels. The resultant pathologies are atherosclerosis and restenosis, which are accelerated, in insulin-resistant type 2 diabetic patients compared with nondiabetic subjects. Controlling glucose to nearly normal levels is crucial to attenuate atherosclerosis. This also prevents and slows the progression of microvascular complications. However, other factors in addition to glucose contribute to atherosclerotic complications. As we begin to understand the cellular changes associated with vascular injury, it is critical to determine whether the inhibition of growth and movement of cells in the vasculature could serve as a novel therapeutic strategy to prevent the vascular complications of diabetes.

The Insulin Resistance Syndrome –

Insulin resistance and diabetes increase the atherosclerotic process. Epidemiological studies demonstrate three- to fourfold increased rates of coronary artery disease mortality in type 2 diabetic patients compared with nondiabetic subjects. Prediabetic patients presenting with impaired glucose tolerance have a two fold increased rate of coronary heart disease mortality compared with subjects with normal glucose control, which suggests that atherosclerosis is enhanced in insulin resistance, even in the absence of frank hyperglycemia. Insulin resistance is associated with a constellation of factors that enhance atherosclerosis. These factors include a common dyslipidemia consisting of an elevated level of triglycerides, a low HDL, and increased oxidized LDL; an increased prevalence of hypertension; an increased thrombotic tendency due to an increased production of plasminogen activator inhibitor-1 (PAI-1) and fibrinogen; and endothelial dysfunction. Hyperinsulinemia paired with insulin resistance may further accelerate vascular injury. Insulin also is a modest vasodilator and stimulates nitric oxide production in endothelial cells. This process is mediated by the phosphatidylinositol 3-kinase (PI3-K) pathway, which also mediates insulin's ability to simulate glucose transport in a variety of tissues, including skeletal muscle and adipose. Insulin-resistant subjects, by definition, are defective in insulin-mediated glucose transport. Mounting evidence also suggests that insulin-resistant subjects have a defect in insulin-stimulated nitric oxide production, which parallels their defect in glucose transport. Altogether, these observations suggest that insulin resistance may be associated with a global defect of PI3-K signaling in response to insulin. In contrast, insulin stimulates vascular cell growth and migration. The mitogen-activated protein kinase (MAPK) pathway appears to function normally in these proatherosclerotic effects of insulin. Similar data in human studies indicate that insulin-resistant subjects have defective PI3-K activity in the skeletal muscle but normal insulin-stimulated MAPK activity. We have hypothesized that an imbalance between these two pathways in the insulin-resistant state shifts the balance toward enhanced proatherosclerotic effects of insulin with decreased nitric oxide activity to accelerate atherosclerotic processes.

Role of Cell Proliferation and Migration in Vascular Disease

Atherosclerosis

Atherogenesis consists of a cascade of events involving interactions of circulating cells and substances within the vascular wall. The first step of this cascade involves damage to the endothelium

caused by traditional cardiovascular risk factors including diabetes. These factors are mediated by the MAPK pathway. In insulin-resistant models, such as the Zukedr obese rat, the vascular PI3-K pathway is attenuated, whereas MAPK activity is enhanced. Insulin resistance, even in the absence of these risk factors, is associated with endothelial dysfunction in the peripheral arterial circulation, as well as in the coronary arterial bed. Endothelial damage results in a lower production of nitric oxide, which inhibits thrombosis, inflammation, and vascular smooth muscle cell (VSMC) growth and migration to prevent the vascular injury response. Another manifestation of injury to the endothelium is the expression of adhesion molecules: intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 promotes the attachment of circulating monocytes, macrophages, and platelets. An inflammatory reaction ensues, along with the production of the chemokines, specifically monocyte chemoattractant protein-1 (MCP-1) which directs migration of the attached monocyte/macrophages into the vascular wall. Clot formation, in addition to inflammation, occurs in the vessel wall. LDL is incorporated into the vessel wall and is phagocytosed by macrophages to form foam cells. This phagocytosis is markedly enhanced when LDL is oxidized. The lipid-laden foam cells break down inside the vessel wall to form fatty streaks. VSMCs migrate from the media to the intima, where they proliferate and form a neointima with increased extracellular matrix production, leading to the development of an organized atherosclerotic plaque. These smooth muscle cell changes are thought to constitute a late event in the atherosclerotic process; however, recent evidence suggests that early formation of neointima may contribute to the enhancement of inflammatory and thrombotic processes, leading to atherosclerosis in the vessel wall.

Subsequently, a critical question emerges: Which step in the atherosclerotic cascade should be targeted to inhibit atherosclerosis? Considerable data from clinical trials indicate that lowering LDL levels has a major impact: it decreases myocardial infarction, stroke, and cardiovascular mortality. Decreasing other risk factors, such as hypertension and hyperglycemia, also significantly attenuates both macrovascular and microvascular diseases in diabetes. Inhibiting the thrombotic reaction with aspirin or other agents, which in turn inhibits platelet function may decrease coronary artery disease events and mortality in subjects without diabetes. The American Diabetes Association has recommended aspirin therapy to prevent cardiovascular disease in patients with diabetes. Recent evidence in genetically altered animal models of atherosclerosis underscores the role of inflammation. A knockout of apolipoprotein E in mice results in the development of hypercholesterolemia and advanced atherosclerotic plaques similar to those seen in humans. These animals can be rescued from atherosclerosis by knockout of either MCP-1 or macrophage colony-stimulating factor, which would prevent the movement of monocytes attached to the endothelial surface into the vessel wall. Thus inhibition of inflammation in the vascular wall may be an important therapeutic target to stop the atherosclerotic process.

Restenosis

When the endothelium is injured by balloon catheterization or stent placement, VSMCs migrate from the medial (and possibly the adventitial) layer to the intimal layer of the vessel wall where they proliferate. The formation of this neointima is an important architectural change in the vessel wall that leads to restenosis after angioplasty or stenting. Neointima formation is accelerated in diabetic patients, who, thus, have increased rates of restenosis compared with nondiabetic patients. Mechanical injury to the vessel wall provokes the release of growth factors that stimulate VSMC movements to, and replication within, the thickening lumina through the activation of key cell signaling pathways, including the MAPK cascade. Reentry of quiescent VSMC into the cell cycle is a hallmark molecular event in the restenotic process. Thus, pharmaceutical interventions targeting VSMC growth or movement are a promising new approach to reduce the risk for restenosis in people with diabetes.

PPAR-γ Expression and Function in the Vasculature

Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a member of the nuclear receptor superfamily, which when activated by ligends, regulates gene expression. Thiazollidinediones (TDZs) bind with high affinity to PPAR-γ to enhance insulin-mediated glucose transport into adipose and skeletal muscle and are clinically used pharmacological ligands. In human and animal models with insulin resistance and type 2 diabetes, TZDs decrease hyperglycemia and hyperinsulinemia. PPAR-γ is expressed abundantly in adipose tissue, where it promotes the adipocyte differentiation and the expression of genes involved in fatty acid metabolism. PPAR-γ is important to normal human physiology. Dorminant-negative mutations of PPAR-γ result in an abnormal ligand-binding domain of the receptor, which inactivates the receptor in humans. This dominant-negative mutation results in the development of severe insulin resistant, type 2 diabetes, and hypertension in the absence of obesity. These patients also exhibited elevated triglycerides and low HDL levels and, thus, expressed a number of components of the metabolic syndrome. In contrast, the presence of a constitutively active receptor in human models results in obseity without insulin resistance or hypertension. These seminal observations suggest that this nuclear receptor is not only important to maintain insulin-mediated glucose transport, but also plays a role in the regulation of vascular tone and potentially other vascular activities.

PPAR-γ is expressed on all major cells of the vasculature, including endothelial cells, VSMCs and monocytes / macrophages. Human coronary artery smooth muscle cells, umbilical artery smooth muscle cells, umbilical endothelial cells, and aortic smooth muscle cells all express PPAR-γ, which is present in nuclear but not cystolic fractions from these cells. In early human atherosclerotic lesions, PPAR-γ expression is present in VSMCs in the neointima as well as in macrophages. In addition, PPAR-γ expression is upregulated in neointima that forms after balloon injury of rat endothelium; these data suggest that PPAR-γ expression is enhanced in vascular cells when the vasculature is damaged. Thus, it is important to define the role of PPAR-γ in vascular injury.

PPAR-γ Inhibits VSMC Profliferation

Pharmacological ligands to PPAR-γ, troglitazone, rosiglitazone, and pfoglitazone all inhibit VSMC proliferation in vitro at drug levels that are achieved when patients are given these agents in antidiabetic doses. Furthermore, examination of the mechanism by which PPAR-γ activation inhibits VSMC proliferation indicates that TZDs block the events that are critical for the reentry of quiescent VSMCs into the cell cycle. This step in the cell cycle requires the formation and activation of cyclin and cyclin-dependent kinase (CDK) complexes that result in phosphorylation of the retinoblastoma (Rb) protein, which functions as a gatekeeper for progression into the DNA synthesis (S phase) segment of the cell cycle. Phosphorylation of Rb releases the sequestered transcription factor E2F, which activates genes that participate in cell cycle progression. CDK inhibitors (CDKIs) $p21^{Cip1}$, $p27^{Kip1}$, and $p15/p15^{NK4}$, regulate this process by inhibiting cyclin/CDK activity and phosphorylation of Rb, resulting in G_1 arrest. We recently found that both troglitazone and rosiglitazone attenuated the mitogen-induced degradation of $p27^{Kip1}$. There was no effect of these agents on levels of cyclins or CDKs. The CDKI$p27^{Kip1}$ negatively regulates growth in a variety of cell types, including VSMCs. Overexpression of $p27^{Kip1}$ inhibits serum-stimulated DNA synthesis in VSMCs, and in a porcine balloon-injury model, $p27^{Kip1}$ expression was markedly reduced in the intima and media after injury. Thus, $p27^{Kip1}$ downregulation is necessary for cell cycle progression, and the activation of PPAR-γ controls cell cycle events through the regulation of this important CDKI.

PPAR-γ Activation Inhibits VSMC Migration

The migration of cells involves 1) attaching to the extracellular matrix, 2) chemotaxis, or locomotion, and 3) burrowing through the extracellular matrix or other barriers. Cells attach to matrix proteins in their environment through cell surface receptors called integrins, which bind to amino acid sequences on the surrounding matrix proteins. Chemotaxis involves the cytoplasmic activation of myosin light-chain kinase and other kinases that are activated by chemoattractants. Invasion allows VSMCs to digest through extracellular matrix as cells move from the media, across the internal elastic lamella, and into the intima. Nuclear events and activation of the MAPK pathway are required for invasion, which involves the production and secretion of matrix metalloproteinases (MMPs). The transcription factor, Ets-q, is known to regulate MMP9 as well as expression of other MMPs. Ets-1 is upregulated by growth factors that activate the extracellular signal-regulated kinase MAPK pathway. Platelet-derived growth factor (PDGF) is a potent chemoattractant for VSMCs. Ets-1 is upregulated by PDGF in VSMCs, which is inhibited by both troglitazone and rosiglitazone. Consistent with their nuclear distribution in cells, PPAR-γ activation does not affect VSMC attachment or locomotion, but it inhibits invasion by transrepression of Ets-1 and subsequent inhibition of MMP production. Thus, activation of PPAR-γ may be an important strategy to control MAPK-mediated VSMC migration.

PPAR-γ In the Macrophage: From Cell Formation Versus Inhibition of Inflammation

PPAR-γ is expressed in monocytes and is upregulated during monocyte differentiation into macrophages. In human atherosclerotic lesions, PPAR-γ expression occurs predominantly in macrophages with lower levels detected in VSMC. The pathophysiological role of PPAR-γ in atherogenesis is a subject of intensive investigation. Early *in vitro* studies of PPAR-γ function in macrophages identified a variety of antinflammatory and, therefore, potentially antiatherogenic activities including the following: an inhibition of cytokine production; an attenuation of cytokine-inducible expression of nitric oxide synthase, gelatinase B1, and scavenger A receptor; and an antagonism of AP-1, signal transducer and activator of transcription (STAT), and nuclear factor-kB transcription activity. The binding of monocytes to proinflammatory adhesion molecules expressed on the surface of endothelial cells and their subsequent infiltration into the subendothelial space may also be negatively regulated by PPAR-γ. The cytokine-induced expression of VCAM-1 and ICAM-1 by endothelial cells and the MCP-1-directed transendothelial migration of monocytes are both potentially inhibited by PPAR-γ ligands. Thus, pharmacological activation of PPAR-γ may suppress some of the earliest cellular events in the pathological sequelae leading to the formation of atherosclerotic lesions. In marked contrast, activation of PPAR-γ in cultured monocytes increased monocyte uptake of oxidized LDL, induced transcription of the scavenger receptor CD36, and promoted monocyte differentiation into foam cells. These actions tend to promote the atherosclerotic process. Clearly, the potentially important role of PPAR-γ in attenuating atherosclerosis can only be defined in vivo.

In Vivo Translation

TZDs improve insulin sensitivity, decrease circulating insulin levels, and lower fasting blood glucose in type 2 diabetic individuals. These changes are associated with reversal of many of the components of the insulin resistance syndrome, including lowered triglycerides, increased HDL, decreased small dense LDL, decreased circulating PA1-1 levels, and decreased blood pressure. These observations suggest that reversal of the insulin resistance syndrome is associated with an improvement in the cardiovascular risk factors associated with insulin resistance. However, activation of PPAR-γ in the vasculature may have direct effects on blood pressure and PA1-1 expression.

Troglitazone was the first TZD demonstrated to prevent neointima formation after endothelial balloon injury of the aorta in rats. Subsequently, pioglitazone was shown to prevent neointima formation in carotid artery injury in rats and to prevent neointima formation in hypertensive rat models. Recently, Tagaki et. al explored these phenomena in humans. They demonstrated that type 2 diabetic patients requiring coronary artery stent placement had less neointima formation 6 months after stent placement if they were on troglitazone plus diet compared with type 2 diabetic patients on diet alone. The patients on troglitazone had decreases in blood glucose compared with those patients on diet alone and significant decreases in fasting insulin levels. Conceivably, metabolic changes could contribute to the differences in neointima formation, although direct effects of troglitazone on the vasculature are also likely to have played an important role.

In the LDL receptor (LDLR) knockout mice, a high-fat diet induces hyperglycemia and hyperinsulinemia; subsequently, the animal served as a model of both atherosclerosis and type 2 diabetes. Troglitazone decreases circulating insulin levels in this model but not in the models presenting with hyperglycemia. A high-fructose diet elevates cholesterol in LDLR knockout mice but does not increase insulin or glucose; therefore, the high-fructose diet is a model of atherosclerosis without diabetes. Administration of troglitazone of the LDLR knockout mice on the high-fructose diets resulted in a 45% decrease in atherosclerotic lesions. Lesions from the troglitazone-treated animals on either a high-fat or high-fructose diet accumulated significantly fewer macrophages than lesions from untreated animals. Rosigliazone and a nonthiazohdinedione PPAR-γ ligand, GW7845, have also recently been shown to suppress atherogenesis in high-fat LDLR knockout mice. Thus, inhibition of macrophage accumulation, and possibly the direct anti-inflammatory effects of TZDs, contributed to the significant attenuation of atherosclerotic lesion formation in this model. Two observations suggest that PPAR-γ ligands may have similar activities in humans. First, troglitazone has been demonstrated to decrease carotid intimal medial wall thickness (IMT) after 3 months of treatment in type 2 diabetic patients. However, this observation was based on only a small number of patients for a short period of time, making it difficult to demonstrate consistent changes in carotid IMT. Second, PPAR-γ ligands have been demonstrated to decrease albuminuria in type 2 diabetic patients when compared with the use of other oral antihyperglycemic agents. When troglitazone or metformin were given for 8 weeks to patients with type 2 diabetes and microalbuminuria, both agents similarly decreased blood glucose and HbA. However, troglitazone, but not metformin, reduced albumin excretion rates. Similarly, when glyburide or rosiglitazone was given to patients with type 2 diabetes and microalbuminuria, rosiglitazone, but not glyburide, was associated with substantial reductions in albumin excretion. Albuminuria is considered not only a marker of nephropathy in type 2 diabetes, but also a marker of widespread vascular disease; as such, it correlates with endothelial dysfunction. Thus the decrease in albumin excretion may not only have implications for renal protectin but for vascular protectin as well. Troglitazone has also been demonstrated to improve endothelial cell dysfunction in patients with insulin resistance and type 2 diabetes. In addition, we demonstrated that troglitazone improved coronary artery endothelial function in insulin-resistant subjects. (*reprinted from Dr. Hsueh's review article which appeared in Diabetes Care, 24:2, 2001)*

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Clinical Update of Viral Hepatitis A-G

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This discussion is a review and update on clinical information that will hopefully be useful in everyday practices and may provide some answers to most commonly asked question by the patients.

Hepatitis A

Hepatitis A (HAV) was identified in 1973 as a small non-enveloped single stranded RNA virus from the picornaviradae family. It is transmitted mainly fecal to oral but can occur from blood contact during the prodrome phase which is usually two weeks before the onset of jaundice. The incubation period is about 28 days and the HAV IgM is detectable 5-10 days after exposure and can persist up to six months. Most patients usually recover and develop life long immunity. However, there is about 12 % relapse and about 2% of the cases will develop into fulminant hepatic failure. The death rate is about 2% for some one over the age of 50 years but this fatality increases to 72 % when there is superinfection of HAV to a patient with HBV and a fatality rate of 40% when there is HCV. There is more than 50 times increase in mortality in patients with chronic hepatitis compare to patients with no history of liver disease. This leads to the importance of HAV vaccination in the Asian population with a high level of chronic hepatitis B.

HAV vaccinations are to be given to people traveling and working in country with high rate of infection, homosexual, intravenous drug users and people with chronic liver disease. The two vaccines that are available are Havrix(SKG) and Vaqta (Merck). There is almost 100% immunity and the vaccine should be injected intramuscularly two times over six month period. The vaccine must be given 3-4 weeks prior to visiting endemic areas. If there is not enough time for the vaccine, passive immunization should be administered. A 0.02 ml/kg of immune globulin should be given for post exposure and for less than three months stay and 0.06 ml/kg for up to six month stay. The vaccine is not recommended for any one younger than two years of age.

Hepatitis B

Hepatitis B (HBV) is the 9th leading cause of death worldwide and there are more than 300 million chronic HBV carriers worldwide. It affects 15-20% of the population in Asia. In United State it affects only 0.1% or 1.2 million people. The disease state is different in Asia and the U.S. This is due to the difference in the age of transmission. In Asia, HBV is vertically transmitted from mother to the infant. Placenta is a potent barrier and transmission occurs at the time of childbirth. Once the baby is infected, 30-90% will become a carrier. In the United State, transmission occurs later in life with experimentation with sex and drug. At this age, only 10% becomes a carrier. The difference in the carrier states may be due to immature immune systems. As a result there are more incidence of hepatocellular carcinoma and cirrhosis in the Asian population.

Hepatitis B can present as acute, fulminant and asymptomatic chronic carrier. There is no recommended therapy for acute hepatitis but Lamivudine has been used in some cases. The treatments

that are discussed are for chronic hepatitis B which by definition is persistently positive HBSAg for greater than six months.

Treatment is recommended for people with positive HBSAg, HBeAg with elevated ALT and viral DNA level. The treatment goal is to achieve seroconversion of HBSAg which is rare or loss of HbeAg which would mean less viral infectivity. Hopefully, this in turn would lead to less cirrhosis and liver cancer.

The two most commonly used treatments are Alfa Interferon (IFN) and Lamivudine. IFN is a family of naturally occurring small protein and glycoprotein which is a product of immune cell response to a viral infection. The mechanism of action is unknown. It is thought to inhibit viral replication, inhibit viral attachment, induce proteases or amplify cytotoxic T-cell. Therefore, people lacking a competent or under developed immune system does not response well to IFN. Patient with high ALT and low pre-treatment DNA level reflecting a good endogenous immune response has a good predictive outcome with IFN. It is given in 5 MU qd or 10 MU TIW for 16 weeks. There is a loss of eAg and DNA in 20-40% and loss of HBSAg in 5-10%.

The other main treatment of HBV consists of nucleoside analogues. They replace naturally occurring nucleoside such as adenosine, guanosine, cytidine, thymidine and uridine, and cause DNA chain termination. Besides Lamivudine, the other nucleoside analogues are Famciclovir(guanosine), Adefovir Dipivoxil(adenosine), Entecavir(guanosine) and Lobucavir(guanosine).These drugs suppress the replication but do not eradicate the HBV. As a result, stopping the medication may lead to relapse.

Lamivudine, an analogue of dideoxycytidine is the nucleoside which has been tested in patients with chronic HBV in long-term trials. There are now data using Lamivudine up to four years. In the initial study, Lamivudine 100 mg per day was given for one year. There was 72% normalization of ALT, 16% HbeAg loss or conversion and 55% improvement in histology. Two-year study revealed 27-38% eAg loss with 52% undected DNA. Three-year study revealed 40% eAg loss and four-year study revealed 47% eAg loss. The seroconversion of HbeAg increases if ALT is >2X normal. The side effects are minimal with reports of pancreatitis and lactic acidosis.

Resistance is a problem with nucleoside analogue and can be seen as elevation of DNA level. This occurs only after 9-12 months use of medication and occurs at a rate of 10-15% per year. With Lamivudine there is a mutation at the YMDD locus with a substitution of either valine or isoleucine for methionine at residue 552. Substitution of this smaller amino acid side chain may enlarge the nucleotide-binding pocket, reducing its affinity for lamivudine. YMDD variants continue to replicate at low level and often induce little or no liver injury. Lamivudine should be continued despite the mutant since there is still evidence of improved biochemical and histological improvement. In the 4-year data consisting of 58 patients, 39 or 69% of the patients developed YMDD mutation. With continued treatment, 13 out of 39 patient loss their eAg.

Lamivudine should be given 100 mg qd with laboratory testing of DNA, ALT, eAg/eAb every month. Medication should be discontinue when there is an eAg loss and recheck labs in 3-6 months. Lamivudine should be restarted if there is an elevation of DNA.

The other area of research has been immunomodulatory therapy where the main focus is activation of T-cell. Thymosin alpha1(Zadaxin) which is a thymic derived peptides to stimulate T cell

function. Interleukin-12 has been used to promote T-helper cell. The use of DNA vaccine as oppose to peptide vaccines can stimulate not only B cell but also T cell response. This can lead to prolong expression of viral proteins.

Hepatitis C

The hepatitis C virus was discovered and named in 1989 by Choo et al. It has long been a cause of post-transfusion hepatitis and was known as non-A, non-B hepatitis.

Chronic hepatitis C effect 170 million people worldwide and 3.9 million people in the United States. It is the main reason for liver transplantation in the United States. Like HBV, it is transmitted via blood and sex. However, the U.S. Public Health Department did not suggest any change in the sexual practice in monogamous relationship. There is a 3% chance of sexual transmission in a monogamous relationship while there is a 10 % chance with high-risk behavior. Homosexual transmission is about 7%. Perinatal transmission is about 5% and increase to about 10-15% when the mother is co-infected with HIV. Like other viruses, the level of viremia dictates the incidence of transmission.

It is a hepacivirus which is a RNA virus with an envelope. It has 9400 base pair and has been difficult to study the virus due to the lack of cell culture and due to the genetic variations. There are six genotypes with many subtypes which will be important for duration of treatment. Genotypes 1-3 occurs through out the world but genotype 4 is found in Egypt while genotype 5 in South Africa and genotype 6 in Asia. This genetic variability has made it difficult to develop a vaccine and there is no treatment for HCV post-exposure since the immune globulin is not effective.

When acute infection occurs, approximately 85% of the patients become a carrier. The incubation period is 2 to 30 weeks and the symptoms can be wide range. The diagnosis can be made with several tests which include the HCV antibody, recombinant immunoblot assay(RIBA) or measurement of HCV viral level. The HCV antibody test is an ELISA and the first generation test only has a sensitivity of 70-80%. There is many false positive and the confirmatory testing such as RIBA and HCV PCR are done.

Current therapy consists of Rebetron, combination Interferon and Ribavirin. The NIH consensus suggests treatment for patient with elevated ALT and RNA with moderate to severe histology with or without fibrosis. Patient with mild histology and cirrhosis should be evaluated in individual cases. Patient with normal ALT and decompensated cirrhosis should not be treated. The best predictors of response are hepatic histology, genotype and pre-treatment viral load.

Randomized trials have shown that Interferon alone for 24 and 48 weeks lead to a sustained response of 6% and 16% respectively. Rebetron for 24 and 48 weeks lead to a sustained response of 33% and 41%. The recommendation is treatment for six months for genotype 2,3 and type 1 with viral load less than 2 million copies/ml. Treatment of 12 months for genotype 1,4 and high viral load greater than 2 million copies/ml.

Newer drugs consist of pegylated interferon which is IFN conjugated one to one with a 12,000 dalton polyethylene glycol molecule. This reduces the clearance of interferon and can be given subcutaneous one time a week as oppose to three times a week. Monotherapy offers a sustain response

of 36% which is still not as good Rebetron. The combined Pegylated interferon and Ribavirin has the best-sustained response rate of about 52-56%.

The future treatment will focus on stopping the viral cycle. They are model after HIV treatment and are inhibitor of protease, helicase and ribozyme. Serine protease inhibitor would block cleavage of non-structural proteins while Helicase inhibitor would stop viral replication and transcription by not allowing the RNA to unwind. The ribozyme cleaves target RNA in specific manner to stop replication.

There are also researches on gene therapy, which is being directed to block protein synthesis by preventing translation. CDNA, a synthetic complementary DNA is made to bind to initiation site of messenger RNA to stop translation. However, there are no adequate delivery systems of the CDNA since the body has many nucleases to breakdown the CDNA.

Current therapy for both hepatitis B and C is adequate for select patients but with newer treatments and combination treatment the future hold optimism for possible eradication of the disease.

Hepatitis D

Hepatitis D (HDV) was first describes in 1977 in Italy and is a defective 36 nm particle with an envelope, HD Ag and single stranded circular RNA. The infections occurs mainly via blood but can be sexually transmitted with a require presence of hepatitis B. It can be a coinfection where the HBV and HDV are simultaneous contracted or superinfection where a HBV carrier is infected with HDV. The clinical importance of coinfection is that it rarely leads to chronic HDV since it depends on the concurrent activity of HBV. In superinfection the hepatitis D is saved by the pre-existing HBSAg and usually leads to chronic hepatitis D. Due to coinfection of two or even three viruses(B,C,D), chronic hepatitis D can result in severe disease and can progress to cirrhosis in 70% of the patients. Hepatitis D is more prevalent among intravenous drug user.

Diagnosis is made by finding HDV antibody in the serum or by finding the HDV RNA or HDV Ag in the liver cells. The treatment consists of Interferon or by treating the HBV.

Hepatitis E

Hepatitis E (HEV) was cloned and sequenced in 1990 and was initially named enterically transmitted non-A, non-B hepatitis. It was first detected in 1983 in feces collected from a patient who was suspected of having enteric non-A, non-B. It is a small non-enveloped 34 nm particle with a single stranded RNA. The gene has been sequenced but the many aspects of the viral life cycle such as attachment, entry, transcription, assembly and release are still unclear. It is endemic in Mexico, India, Southeast and central Asia and there have only been two reported cases in the United States. There are two distinct strains (Asian and Mexican) with a 75% homology of the gene. It is transmitted fecal-oral route with an incubation period of about two to ten weeks. Diagnosis is usually made by checking for Anti-HEV IgM and IgG. Clinical presentation is similar to other viral hepatitis and is a self-limiting disease which last 1-4 weeks. The mortality rate is low(0.07-0.6%) except in a pregnant woman in her third trimester, where there is a 25% mortality rate. There is no associated chronic hepatitis, cirrhosis or liver cancer. Passive immunity is not useful and vaccine is in the works for traveler going to endemic area

Hepatitis G

After the discovery of HCV, there were still cases of unexplained post transfusion hepatitis. This led to looking for non-A,B,C hepatitis and the initial interest was sparked by the serum of a surgeon who acquired hepatitis which was non-A, B or C. Hepatitis G (HGV) is a virus that is similar to the Flaviviridae family with a single stranded RNA(+) virus. The gene was sequenced in 1997 and is detected by ELISA for theE2 envelope or by PCR assay. It was discovered in 24% of intravenous drug user and in 2% of blood donor in the United States. Due to the self-limiting nature and acquisition of immunity, the research in HGV has slowed down. The most interesting to have come out in the past five years is that it does not cause major liver disease. It is equally present in post transfusion blood tests of patients with elevated transaminases or with normal transaminases.

This has lead to a decision not to screen the worldwide blood supply since there is not enough evidence to suggest any benefits to the recipients. To screen for a new agent it has to be transfusion related transmission, must cause an adverse reaction in the recipient and a screening test must be available. In the meantime, the search continues for other viral hepatitis.

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RECENT DEVELOPMENTS IN THE TREATMENT OF DIABETIC MACULAR EDEMA

Stanley Chang, M.D.

Diabetic macular edema is the most common cause of moderate visual loss in patients with diabetes. It is believed that macular edema accounts for approximately 50% of patients with diabetes with symptoms of blurred vision seeking care in an eye clinic. Macular edema may be the first symptom of diabetic retinopathy and may be associated with proliferative or non-proliferative (background) retinopathy. Based on data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), it is estimated that, of approximately 7.8 million patients affected with diabetes in 1993, 95,000 are expected to develop macular edema annually. This problem presents a significant form of impairment for working patients with diabetes since it may affect their ability to read and to drive and to maintain a productive career.

Macular edema results from the breakdown of the blood-retinal barrier in the retinal capillaries. The tight endothelial cell junctions break down resulting in increased vascular permeability and increased fluid accumulation in the outer layers of the retina. Microaneurysms are believed to play a significant role by acting as sources for fluid and lipid transudation. Factors that are believed to cause the formation of microaneurysms are loss of pericytes and supporting astrocytes in the retina, increased capillary transmural pressure, and local production of vasoproliferative factors such as vascular endothelia growth factor (VEGF). Hyperglycemia is believed to be the main factor that causes increased oxidative stress, the accumulation of advanced glycation endproducts, and generation of diacylglycerol. The substances activates protein kinase C which in turn increases VEGF expression.

Clinically the findings in patients with diabetic macular edema are micraneurysms, dot and blot hemorrhages, and lipid (hard) exudates. These result in areas of retinal thickening around the macula and cystic changes in the macula. In advanced stages, there may be atrophy of the pigment epithelium or fibrous changes within the central foveal area. Sometimes lipid deposits surround a group of actively leaking microaneurysms in a circinate pattern (circinate rings). When exudates occupy the foveal area it is believed that permanent visual loss will occur even if the exudates reabsorb after treatment. In other cases, diffuse macular edema may also occur. In this condition there is diffuse leakage from capillaries surrounding the macular, without identifying specific focal areas of leakage. This type of edema is more recalcitrant to treatment by laser photocoagulation. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined the term "clinically significant macular edema" to include the following characteristics:

1. Thickening of the retina at or within 500 microns of the center of the macula
2. Hard exudates at or within 500 microns of the center of the macula if associated with thickening of the adjacent retina
3. A zone or zones of retinal thickening 1 disk diameter (DD) or larger, any part of which is within 1DD of the center of the macula

Fluorescein angiography is used in the diagnosis and treatment of diabetic macular edema. The dye is injected intravenously and demonstrates the retinal capillary circulation and areas of increased vascular permeability that is associated with macular edema. This is used to guide laser therapy when indicated. A new diagnostic modality most useful in the diagnosis and treatment of macular edema is optical coherence tomography (OCT). This modality uses a low intensity infrared laser to scan the

retina, and using reflectance interferometry, images of the retina are obtained that appear similar to a histologic section of the macula. In diabetic macular edema, the macular thickness can be several times normal and the cystic spaces of fluid accumulation are easily demonstrated. This tool is gradually replacing most methods of assessing the treatment response to any treatment modality for diabetic macular edema.

Systemic factors that may contribute to the progression of diabetic retinopathy and macular edema are blood glucose control, hypertension, and nephropathy and proteinuria. The Diabetes Control and Complications Trial (DCCT), a randomized, controlled clinical trial involving 1441 patients demonstrated that improved glucose control resulted in a lower rate of progression of diabetic retinopathy, a lower incidence of clinically significant macular edema, and less frequent need for laser photocoagulation. The United Kingdom Prospective Diabetes Study (UKPDS) showed in type 2 diabetes that better glucose control over a twelve year period reduced the progression of retinopathy from 48.7% to 38.6%. Tight control of blood pressure with atenolol or an angiotensin converting enzyme inhibitor reduced the progression of diabetic retinopathy by 34% and a reduction of visual loss by 47% over a 7.5 year period. While little can be done to control the rate of progression of proteinuria, it seems prudent to consider the use of an ACE-inhibitor and frequently monitor the blood pressure in patients with diabetic retinopathy and nephropathy.

The classic form of treatment of for diabetic macular edema is laser photocoagulation. The ETDRS showed that focal/grid photocoagulation reduced the rate of moderate visual acuity loss by 50% in patients with CSME. Moderate visual loss is defined as a doubling of the visual angle, e.g. from 20/40 to 20/80. However while laser photocoagulation reduced the rate of progression of visual loss, once visual acuity was already reduced, eyes treated with laser were unlikely to improve to 20/40 or better. Also, the degree of visual gain following laser is moderate, and may take months to occur. These observations have led to the search for other new approaches for the treatment of diabetic macular edema, both primary cases and those not responding to laser photocoagulation.

In some cases it is believed that vitreous traction plays a role in the development of DME. A thin epiretinal membrane forms on the retinal surface resulting in tangential traction. Surgical removal of the membrane has resulted in reduction of edema and a modest improvement of visual acuity.

More promising is the pharmacologic treatment of diabetic retinopathy. Currently clinical trials are in progress to study the efficacy and safety of PKC inhibitors administered systemically. Early reports appear promising. In addition, recent trials are starting for local treatment of diabetic macular edema using intravitreal injection of triamcinolone. These new treatment modalities offer potential for medical treatment and possibly better visual outcomes.

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State of the Art: Congenital Heart Disease 2002

Daphne Hsu, M.D.

The following is a summary from the Power Point slides of Dr. Hsu's presentation

New Advances in Pediatric Cardiology

- ¶ Management of the infant with congenital heart disease
  - Fetal enchocardiography
  - Infant surgery
  - Heart transplantation
  - Hypoplastic left heart syndrome
- ¶ Interventional Cardiology

Fetal Ultrasound

- ¶ Cardiac development
  - 6 weeks gestation: heart chambers, great arteries formed.
  - 14 weeks: major cardiac defects can be detected by ultrasound.
  - 22-24 weeks: most common time for abnormalities to be identified.
- ¶ Cardiac screening
  - 4 chamber view
  - 2 great arteries

Fetal Echocardiography

- ¶ Ventricular hypoplasia
  - Tricuspid atresia
  - Hypoplastic left heart syndrome
  - Single ventricle
- ¶ Atrioventricular canal defect, VSD
- ¶ Transposition of the great arteries
- ¶ Pulmonary or aortic valve stenosis
- ¶ Tetrology of Fallot
- ¶ Coarctation of the aorta, ASD cannot be ruled out
- ¶ Ventricular function
  - Congenital defects
  - Arrhythmias
    - SVT
    - Heart block
- ¶ Follow-up studies may detect progression of defect
  - Vavlvar stenosis - atresia
  - Progressive ventricular hypoplasia

Motality associated with congenital heart disease in the United States

- Boneva *et al*. Circulation 2001
- National Center for Health Statistics of the CDC from 1979-1997
- Mortality from heart defects declined 39% over the 18 years period at all ages
  2.5 to 1.5 per 100,000 population
  2.7% per year

Factors influencing improved infant survival

- Echocardiographic diagnosis
  Diagnostic catheterization 5%
- Prostaglandin E
- Surgical techniques
- Post-operative care
- Fetal echocardiography?

Impact of fetal diagnosis

- Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome (*Tworetzky et al, circulation 2001*)
- Patient population: 88 patients
  Prenatal 33
  Postnatal 55

Surgiacal Interventions in HLHS

- Single ventricle palliation: 3 stages
  - Systemic venous return directly to lungs bypassing the heart, RV supplies blood flow to the body.
  - Infancy: single RV with BT shunt (Norwood)
  - 8 months: SVC to pulmonary artery connection
  - 3 yrs: IVC to pulmonary artery connection
- Heart transplantation

Outcome: Staged palliation for HLHS

- Norwood Stage 1 30-45%
- SVC-PA connection 4%
- IVC-PA connection 4%
- Overall 5 year survival 50%

Mortality on Heart Transplant Waiting List

- 16% children>6 months (n=497)
- 25% infants <6 months (n=639)

Decision Analysis of HLHS Treatment Strategies

- A comparison of treatment strategies for HLHS using decision analysis (*Jenkins et al. J Am Coll Card 2001)*
- Pooled data from 5 centers: surgical mortality for staged surgery not increased if performed within one month of age

Treatment Strategies

Name	Description of surgery
Staged surgery	Stage 1 and 2 performed
Stage 1, the list	Stage 1 performed, then listed, receives organ if available
List, wait 1 month	If organ not found within 1 month, Stage 1 then Stage 2
List, wait 2 months	As above for 2 months
List, wait 3 months	As above for 2 months
List, wait until transplant	Pt waits until organ is available

Increasing the Donor Pool: ABO Incompatible Transplant

- Hearts allocated by blood type compatibility
  - O: Universal donor- recipient O, A or B
  - Type O recipients more likely to die while waiting
  - A,B hearts not used if recipient not available
- Fetus synthesizes IgM (agglutinins)
- Neonate: Anti-A and Bare IgG of maternal origin
- Production of anti-A and B agglutinins begins at 3-6 months
- Anti-A and B titers maximal levels by 5-10 yrs
- Hypothesis: Neonates would be tolerant of an ABO incompatible donor due to the absence of IgG anti-A and anti-B agglutinins
- Nost common mismatch: Recipient O, Donor A,B

ABO Incompatible Heart Transplants: Hospital for Sick Children: NEJM 2001

- 10 ABO incompatible transplants performed between 1996 and 2000
- Survival 80%, comparable to ABO compatible
- No hyperacute rejection
- Mild humoral rejection noted at autopsy in one infant w/antibodies
- 2 infants developed antibodies to donor antigens but no evidence of damage to graft
- Mortality on waiting list declined from 58% (1990-96) to 7% (1996-2000)

Post-transplant Management

- Routine immunosupression
- Normal rejection surveillance: clinical and endomyocardial biopsy
- ABO antibody titer surveillance - titers = or > 1.4 consider plasmpheresis and increased immunosupression
- coronary angiography performed 6 and 12 months from DOT, then annually

Patient DS: blood type O

- HLHS, poor RV function, tricuspid insufficiency and LV thrombus
- Intubated on prostaglandins
- Heart transplant at 17 days of age: Donor type B
- Discharged post-op day #14
- One episode of clinical rejection, treated with increased immunosuppression
- All anti B antibody titers negative to date

New Advances in Interventional Cardiology

- Therapeutic Catheter Interventions
  - Alterative to surgery
  - Adjunct to surgery
- Implantable Devices
  - Open: Stent
  - Close: PDA, ASD, VSD

Intravascular Stent

- Stenosis not amenable to balloon dilation
  - Post-surgical
    - Branch pulmonary arteries
    - RV-PA conduit
    - Re-Coarctation
    - Venous baffles
  - Native
    - Coarctation
    - Peripheral pulmonary stenosis

PDA Closure Devices

- Gianturco Coil
  - Ductus < 2 mm
  - Hourglass appearance
- Clinical trial: Amplatzer Ductal Occluder
  - Larger PDA > 2 mm
  - Any anatomic subtype

Amplatzer PDA Occluder: *Children's Hospital of NY (4/00 - 1/02)*

- 62 pts: I mos to 71 yrs
- 6 pts excluded: PDA too small, coil closure- 5 pts
  Irreversible pulmonary hypertension- 1 pt
- 56 successful implantations
- Ductus size: 3.5 mm (1.8-10 mm)
- Closure rate: 53/66 (94.6%) closed at discharge, 55/56 (98/2%) closed on last follow-up

ASD Closure Devices

- Two devices are FDA approved
- Cardioseal
  - Lower profile
  - Stainless steel/Dacron
- Amplatzer Septal Occluder
  - Easily retrievable
  - Optimal for larger defects

Clinical Applications of Transcatheter ASD Closure

- Secundum ASD
  - Isolated
  - Multiple
  - Standard of care shifting
- Patent Foramen Ovale with paradoxical embolus
- Fontan Fenestration

Future Directions in Pediatric Cardiology

- Biomechanical devices
  - Valves
  - Growth potential
- Evidence based medicine
  - NHLB/NIH funded Pediatric Heart Disease Clinical Research Network
  - 7 Centers in US and Canada
  - Encourage multicenter trials in children with heart disease
  - Clinical outcomes: medical, catheter-based and surgical therapies

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Fabry Disease: from Molecular Diagnosis to Enzyme Therapy

Yeong-Hau H. Lien, MD, PhD

Fabry disease is a rare genetic disease due to a deficiency of the lysosomal hydrolase α-galactosidase A (α-Gal A) [1]. The recent advance of knowledge in Fabry disease can be applied to other lysosomal diseases and enhance our understanding in the pathogenesis and management of those once considered miserable and untreatable diseases. Unlike other lysosomal diseases, Fabry disease involves multiple organ systems and may have an onset at a wide range of age [2], therefore, it may be encountered by a variety of medical professionals, such as:

Nephrologists for proteinuria and chronic renal failure
Dermatologists for angiokeratoma
Cardiologists for cardiomyopathy, valvular disease, heart failure, and arrhythmia
Neurologists for neuropathic pain and strokes
Ophthalmologists for corneal opacity and cataracts
Pediatricians for febrile illness, exercise intolerance
Primary care physicians for pain, weakness, heat and cold intolerance
Otolaryngologists for hearing loss and tinnitus
Rheumatologists for joint pain and fever

The diagnosis of Fabry disease has been a challenge to physicians. The misdiagnoses have been included:

Systemic lupus erythematosus
Focal glomerulosclerosis
Familial or idiopathic cardiomyopathy
Coronary artery disease
Strokes
Multiple sclerosis
Fibromyalgia
Erythromelalgia
Raynaud's syndrome
Rheumatic fever
Rheumatoid arthritis
Neurosis
Growing pain
Malingering

Fabry disease is an X-linked disease, thus it manifests primarily in affected hemizygous males and to some extent in heterozygous (carrier) females. Traditionally, the diagnosis is made by measuring α-Gal A activity in plasma, leukocytes, or skin fibroblasts. However, female carriers can have α-Gal A activity ranged from barely detectable to normal [2]. For this reason, recently, molecular diagnosis or mutation analysis has emerged as an important diagnostic tool for Fabry disease. We routinely perform direct sequencing on RT-PCR product using mRNA isolated from 4-ml whole blood. We identified mutations in 10 unrelated families including one novel mutation (R301G) and 9 previously reported mutations (P40S, R112C, N215S, R301Q, R220X, R227X, 777delA, 1188delC and IVS1-1G>C). From 22 individuals at risk (most of them have heterozygote mother) of 6 unrelated

families, we diagnosed 4 male patients and 7 female carriers [3]. The same technique can be used for prenatal diagnosis.

Knowledge of the patient's mutation and its molecular consequences may have practical relevance. Currently, efforts to establish genotype/phenotype correlations have been limited, because most Fabry disease patients have private mutations. Worldwide Fabry registry studies that follow Fabry disease patients with known genotypes for a prolonged period of time would provide important information to establish genotype/phenotype correlation. Prediction of the clinical phenotype on the basis of type or location of a molecular lesion is also premature, as information on structure-function relationships is incomplete. Most genotypes (93%) are associated with classic Fabry disease. Genotypes with nonsense and frame-shift mutations, which cause a premature termination of protein synthesis, are associated with classic Fabry disease. Many missense mutations involving catalytic sites, dimerization sites, or protein folding also correlate to classic Fabry disease. So far, only 18 genotypes have been reported to be associated with cardiac variant Fabry disease, in which patients only have cardiomyopathy and proteinuria. All except one (an in-frame shift with 3-nucleotide deletion) are missense mutations. Several of them cause protein instability due to improper protein folding, and one alters the glycosylation site (N215S). Interestingly, 4 genotypes (R112H, R301Q, G328R and R404del) have been reported to be associated with cardiac variant Fabry disease in one family, but classic Fabry disease in the other [2].

The most exciting development in Fabry disease is the availability of enzyme replacement therapy [4,5]. Two products have been developed independently: Fabrazyme (Genzyme) and Replagal (Transkaryotic Therapies). Both have been available in Europe and other countries, but not in the United States. Fabrazyme is manufactured in Chinese hamster ovarian cells, while Replagal in human fibroblasts. Chemically, the glycosylation patterns are different between the two. Fabrazyme is given at 1.0 mg/kg over 4 hours, and Replagal 0.2 mg/kg over 40 min, every other week. As for safety profiles, both cause infusion reactions such as fever, chills, headache and rigors, which are not uncommon in other types of protein therapies. Both induce antibodies against α-Gal A, but the development of antibodies does not appear to affect therapies and the titers of antibodies seem to decrease over time. The initial studies show that Fabrazyme significantly reduces globotriaosylceramide levels (undegraded α-Gal A substrate) in plasma and endothelial cells, but have no significant clinical effects on renal function, pain relief and quality of life [4]. Replagal appears to reduce neuropathic pain and preserve renal function [5]. Clinical trials are ongoing for both enzymes and will provide more information on the efficacy and safety properties.

Although the enzyme replacement therapy is promising, the requirement of frequent infusions and the enormous cost for life-long therapy make gene therapy an attractive alternative solution. Gene therapy has been tried on a α-galactosidase A knockout mouse model. The adenoviral vector based gene therapy was able to increase α-galactosidase A activity transiently. The globotriaosylceramide storage in tissues was reduced to near normal range for up to 6 months [6]. In our lab, we tested whether RNA/DNA chimeric oligonucleotides can be used to correct point mutation in Fabry cells. Our preliminary data showed that the point mutations in the α-galactosidase A gene can be converted with this approach in cultured Fabry cells [7] and suggested that it may be a promising modality for Fabry disease.

In conclusion, Fabry disease is a fascinating disease, which can mimic many other diseases. Molecular diagnosis for Fabry disease is available and useful for early and prenatal diagnosis as well as detection of female carriers. Enzyme replacement therapy is promising and will be available in the

United States soon. Gene therapy is currently under development and may be the ideal therapy for Fabry disease in the future.

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COPD : STATE OF THE ART

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common diseases that affect many people around the world, including the Chinese in North America. Precise prevalence, mortality and morbidity figures are not available. But, whatever figures available are most likely underestimated because the disease is often not recognized until it is moderately advanced. In the U.S., the prevalence has been increasing. An estimated 17 million peoples in the U.S. are diagnosed with COPD, and probably similar number are undiagnosed. COPD is now the fourth leading cause of death in the U.S. It is the only major chronic disease that is currently on the rise in prevalence and mortality. The WHO predicts that by 2020, COPD will rise from its current ranking as the 12th most prevalent disease worldwide to the 5th, and from the 6th most common cause of death to the 3rd. Health care costs due to COPD are staggering. In 1993, COPD accounted for $ 14.7 billion in U.S. health care direct costs, plus an additional $9.2 billion in indirect costs. Therapy for COPD patients, in particular those with advanced stage, is generally disappointing, and frustrated for both the doctors and patients. The relentless progression of the disease leaves the patient short of breath and debilitated. However, with the rapid advances in medical research and discovery in recent years, we now have a better understanding of the disease, leading to a more refined new definition of the disease and a few new treatment options. Today's discussion will focus on these recent advances about COPD.

DEFINITION

For many years, there have been different definitions of COPD. These make comparisons studies, such as prevalence, treatment success, and health care costs very difficult. To help clarify its diagnosis and recognition, The committee of the recently formed The Global Initiative for Chronic Obstructive Lung Disease (GOLD) developed a working consensus definition of COPD: "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases". It encompasses chronic bronchitis and emphysema. Most patients with COPD have both chronic bronchitis and emphysema, but to different extent.

PATHOGENESIS

- Chronic inflammation – It is now clear that COPD is characterized by chronic inflammation throughout the airway, parenchyma and pulmonary vasculature. This inflammation is caused by exposure to inhaled noxious particles and gases from the various environmental risk factors. This inflammatory process is markedly different from that in asthma. Macrophages, T-lymphocytes (predominantly CD8+), and neutrophils are the inflammatory cells that are increased in COPD. Mediators involved in COPD include leukotriene B4 (LTB4), interleukin 8 (IL-8), and tumor necrosis factor-*a* (TNF-*a*). There is probably complex interaction between cells and mediators,

resulting in progressive obstructive changes in small airways and destruction of lung parenchyma in COPD.

- Protease-antiprotease imbalance – Proteases thought to cause emphysema, are normally counteracted by antiproteases. When there is an imbalance, e.g. in alpha-1 antitrypsin deficiency, emphysema develops.
- Oxidative stress – Oxidative stress may exacerbate COPD through several mechanisms, including the activation of the transcription factor nuclear factor-*k*B (NF-*k*B), which switches on the genes for TNF-*a*, interleukin-8, and other inflammatory proteins, and oxidative damage of antiproteases, such as alpha-1-antitrypsin and secretory leukoprotease inhibitor, thus enhancing inflammation and proteolytic injury.

DIAGNOSIS

A diagnosis of COPD should be considered in any patient who has the characteristic symptoms of chronic cough, chronic sputum production or dyspnea, and/or a history of exposure to risk factors for the disease, especially cigarette smoking. Physical examination is rarely diagnostic in COPD. Signs of airflow limitation are rarely present until the disease is at its advanced stages. Diagnosis of COPD is established by the presence of airflow limitation on spirometry measurement. Patients with COPD typically show a decrease in both FEV1 (forced expiratory volume in one second) and FVC (forced vital capacity), but FEV1is more affected. A post-bronchodilator FEV1 < 80% of the predicted value with a FEV1/FVC < 70% confirms the presence of airflow limitation that is not fully reversible, and thus establish the diagnosis of COPD. The FEV1/FVC is a more sensitive measure of airflow limitation, and a FEV1/FVC < 70% is considered an early sign of airflow limitation in patient whose FEV1 remains normal (> or = 80% of predicted).

Classification of COPD by Severity

The degree of spirometric abnormality generally reflects the severity of COPD. But the relationship between symptoms and the degree of airflow limitation is not perfect. Therefore, to assess the severity of the disease and develop a management plan for individual patient, both symptom and spirometry value should be considered. GOLD proposed the classification of COPD severity into four stages as shown in Table 1.

Table 1: Classification of COPD by Severity

STAGE	CHARACTERISTICS
At Risk	• Normal spirometry • Chronic symptoms (cough, sputum production)
Mild COPD	• FEV1/FVC < 70% • FEV1 > or = 80% predicted • With or without chronic symptoms (cough, sputum production)
Moderate COPD	• FEV1/FVC < 70% • 30% < or = FEV1 < 80% predicted (IIA: 50% < or = FEV1 < 80%) (IIB: 30% < or = FEV1 < 50%) • With or without chronic symptoms (cough, sputum, dyspnea)

STAGE	CHARACTERISTICS
III: Severe COPD	• FEV1/FVC < 70% • FEV1< 30% predicted or FEV1 < 50% predicted plus respiratory failure or clinical signs of right heart failure

SELECTED TREATMENT MODALITIES

Risk Reduction

Reducing the risk factors that cause COPD, in particular the environmental factors, is important in preventing the onset and progression of COPD. Smoking cessation is the single most important, effective, and cost-effective therapeutic intervention to reduce the risk of developing COPD and to slow its progression. It is the only therapeutic intervention that can lessen or stop the rate of progression of COPD. Smoking cessation is crucial in the management of all stages of COPD, and patients should be encouraged to quit as soon as possible. It has been documented that mild pulmonary function abnormalities are completely reversible in smokers who have been smoking for a relatively short duration.

Bronchodilators

Bronchodilator medications are central to the management of COPD. These agents include sympathomimetic drugs (*B*-agonists), anticholinergic agents, and theophylline. There is ample evidence supporting the usefulness of these agents in relieving symptoms associated with COPD. Failure to respond to a single dose of bronchodilator on initial spirometric testing does not signify fixed airway obstruction. All these bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV1.

- Sympathomimetic Drugs – These agents have been the mainstays of treatment for COPD. *B*-2 agonists, with fewer cardiac side effects, are the drugs of choice. Because of their rapid onset of action, they are preferred in treating acute bronchospasm. The inhaled route of administration is preferred in order to maximize beneficial effects and minimize systemic adverse effects. Obtaining the maximal benefit from an aerosol MDI (meter-dose inhaler) requires the proper use of the device. It is imperative that proper techniques be demonstrated to the patient. If necessary, a spacer can be employed. The new dry powder inhaler is breath-activated, and therefore, no hand-breath coordination is required for its use. It is more user friendly. The long acting preparations, salmeterol and formoterol, have recently been shown to be effective bronchodilators in COPD. They have the advantage of twice daily dosing. Tachyphylaxis has not been shown.

- Anticholinergic Agents – These agents are effective bronchodilators in the treatment of COPD. Ipratropium bromide is a synthetic derivative of atropine given by inhalation. It has a slower onset and longer duration of action when compared to short-acting *B*-2-agonists. A long-acting anticholinergic agent, tiotropium bromide, was recently released, but not yet available in the U.S. Tiopropium is very long acting due to its affinity to M3 receptors. Studies have demonstrated that FEV1 is significantly better in patients on tiotropium when compared with placebo.

- Theophylline – Although the use of theophylline in the treatment of COPD is controversial, mainly because of its narrow therapeutic index, several studies have shown that theophylline provides clear benefits to patients with COPD. When used appropriately, theophylline remains a useful drug in the management of COPD. Recognizing its potential toxicity, patients should be treated with lower dosage, aiming for serum levels of 8-12 *u*g/ml.

Combination therapy of bronchodilators with different mechanisms of action produces more bronchodilation than single drug alone. It can also be used to lessen side effects of medications. Therefore, combination of a *B*-2 agonist, an anticholinergic, and/or theophylline can be employed to achieve additional improvements in lung function and quality of life.

Corticosteroids

Both systemic and inhaled corticosteroids have been proven to be effective and beneficial in the treatment of bronchial asthma. However, their efficacy in COPD is not as clear-cut. There are studies that have shown objective improvement in airway obstruction in some patients receiving systemic corticosteroids. Similarly, there are reports showing definitive improvement in airflow obstruction, airway inflammation, and symptoms with inhaled corticosteroids in COPD. But they do not slow the rate of decline in FEV1 in these patients. Many existing COPD guidelines recommend the use of a short course (2-3 weeks) of systemic corticosteroids to identify COPD patients who might benefit form long-term treatment with systemic or inhaled corticosteroids. But there is increasing evidence that it is a poor predictor of the long-term response to inhaled corticosteroids. Instead, the present guidelines recommend a trial of 6 weeks to 3 months with inhaled corticosteroids to identify such patients. Regular treatment with inhaled corticosteroid is only appropriate for symptomatic COPD patient with a documented spirometric response, or in those with a FEV1 < 50% of predicted (stage IIB and stage III COPD) and repeated exacerbations requiring treatment with antibiotics or systemic corticosteroids. Systemic corticosteroids are mainly used during acute exacerbations of COPD. Long-term treatment with oral systemic corticosteroids is not recommended in COPD.

Long-term Supplemental Oxygen Therapy

Studies have repeatedly confirmed the benefits of long-term oxygen therapy in the management of patient with severe COPD. It is the only therapy that increases the survival in hypoxemic patients with COPD, in addition to improving their symptoms and quality of life. The goal is to maintain a PaO2 of at least 60 mmHg (SaO2 of 90%). Indications for long-term oxygen therapy are listed in Table 2.

Table 2: Indications for Long-term Oxygen Therapy in COPD

At Rest (room air)	PaO2 = or < 55 mmHg; or SaO2 = or < 88% PaO2 = 56-59 mmHg; or SaO2 = 89%; with: hematocrit >56%, or cor pulmonale, or right heart failure
During Exercise (room air)	PaO2 = or < 55 mmHg; or SaO2 = or < 88%
During Sleep (room air)	PaO2 = or < 55 mmHg; or SaO2 = or < 88% PaO2 drop > 10 mmHg; or SaO2 drop > 5%; with symptoms and signs of hypoxemia

Pulmonary Rehabilitation

Pulmonary rehabilitation attempts to get patients back to their best possible functional capacity. Many studies have confirmed the overall usefulness of a comprehensive pulmonary rehabilitation program. The benefits include improvement in dyspnea, exercise endurance, and quality of life. It may also decrease the rate of repeated hospitalization and total hospital days. However, pulmonary rehabilitation does not usually improve lung function. For many years, pulmonary rehabilitation was not covered by medical insurance. But starting November 2001, it is now covered by Medicare in New York State.

Surgical Treatments

There is no pharmacological treatment for emphysema and the component of airway obstruction resulting from loss of elastic recoil in emphysema. The disease process is irreversible. Therefore, it is logical to explore surgical approach.

Bullectomy

Bullectomy has been proven effective in patient with bullous emphysema, who has a giant bulla or bilateral bullae, with dyspea and obstructive airway dysfunction. Giant bulla is defined as bulla that occupies at least on-third of the hemithorax. Bullectomy can be done via standard thoracotomy or VATS (video-assisted thoracic surgery). The improvement in lung function and dyspnea tends to correlate with the size of the bullae, that is, the larger the bulla(e), the better the improvement after surgery.

Lung Volume Reduction Surgery (LVRS)

LVRS is a surgical procedure, specifically designed for patients with severe emphysema. Dr. Otto Brantigan pioneered the surgery in the 1950's. Despite symptomatic improvement, the operation was abandoned due to high post-operative mortality rate. With recent advances in surgical technique, Dr. Joel Cooper in St. Louis reintroduced LVRS in 1993. Surgery involves removing 20-30% of the most diseased part of the emphysema lungs. Data from several studies, including our own at Columbia-Presbyterian Medical Center, showed that carefully selected patients with emphysema do benefit from LVRS. In successful cases, following LVRS, there is objective improvement in pulmonary function (including arterial oxygenation), dyspnea, exercise capacity, and quality of life indices. Patients with localized upper lobe emphysema appear to do the best. Data from several studies have shown that the improvement seems to last for 3-4 years. Most patients started to have deteriorating pulmonary function after 3-4 years post-LVRS. But symptomatically and objectively, they are still better than prior to LVRS.

Probable mechanisms of improvement with LVRS include:

- Improved lung and chest wall mechanics
- Improved respiratory muscle function
- Decompression of relatively more normal lung

Because of the uncertainty of the risk of LVRS, the magnitude and duration of its benefit, and the selection of optimal candidate, as well as many other unanswered questions and cost, Medicare stopped paying for the procedure in 12/95. HCFA and NIH began a multi-center, randomized trial to evaluate this surgery, the National Emphysema Treatment Trial (NETT). In this trial, patients are

randomized to best medical treatment for 5 years, or best medical treatment plus LVRS. The study is still ongoing. But the safety monitoring board of NETT released a preliminary finding a few months ago. It reported a subgroup of patients in the trial who are at substantial increased risk for death if they undergo LVRS. The article is somewhat misleadingly entitled, "Patients at High Risk of Death after LVRS". The characteristics of patients at high risk were FEV1< or = 20% of predicted, and either DLco < or = 20% of predicted, or homogeneous distribution of emphysema on high resolution CT scan. The 30-day mortality for the patients treated surgically in the small group was 16%, while that of the medically treated group was zero. It is important not to assume the result of the majority of patients enter into the NETT trial. The final results of the NETT are not yet available. But for now, NETT has clearly shown that patients with FEV1 of < or = 20% of predicted who has either homogeneous pattern of emphysema on HRCT, or DLco of < or = 20% of predicted should not be operated on.

Lung Transplantation

Lung transplantation is now considered a very viable therapeutic modality in patients with very advanced COPD. In appropriately selected patients, lung transplantation has been shown to improve quality of life and functional capacity. Single lung transplantation is the most common procedure for COPD (emphysema).

GENERAL APPROACH TO CURRENT MANAGEMENT OF COPD

With the new understanding of the disease process, a new approach of management should be adopted. Treatment regimen should be initiated according to the severity of the disease, using the new proposed staging system as a guide. After the diagnosis of COPD is established, education about the disease should be undertaken, so that the patient has a better understanding of the illness and can take an active role in its management. Avoidance of risk factors should be instituted. Smoking cessation should be emphasized and demanded. Influenza and pneumococcal vaccine should be given routinely to COPD patients of all stages. Pharmacotherapy is recommended in patients who are symptomatic. It should be instituted in a stepwise fashion according to the severity of symptoms and stage of the disease. Recommended treatment at each stage of COPD according to the GOLD guideline is shown in Table 3. In mild stage I disease, short-acting bronchodilator, such as a *B*-2-agonist, can be given on an as needed basis for intermittent symptoms. When symptoms are more persistent, or in stage II disease, regular treatment with one or more bronchodilators can be used. Inhaled corticosteroids can be tried when symptoms are significant. If there is positive response in symptoms or lung function, inhaled corticosteroids can be continued on a regular basis. In stage IIB or stage III disease, when there are repeated exacerbations, inhaled corticosteroids should be part of the regular regimen in an attempt to reduce the frequency of exacerbations. Pulmonary rehabilitation should be part of the treatment program in patients at all stages of disease, particularly those who remain symptomatic and are restricted in their daily activities despite maximal pharmacotherapy. When excessive secretions are present, measures to mobilize them, such as chest physiotherapy, can be instituted. Long-term oxygen therapy is indicated in patients with hypoxemia. For appropriate candidates, surgical treatment with bullectomy, lung volume reduction surgery, or lung transplantation should be considered. Close attention to psychosocial problems and their appropriate treatment is also important in the overall management of patients with COPD.

Table 3: Therapy of COPD

STAGE	RECOMMENDED TREATMENT
All	• Avoidance of risk factors • Influenza and pneumococcal vaccination
0: At risk	
I: Mild COPD	• Short-acting bronchodilator when needed
IIA: Moderate COPD	• Regular treatment with one or more bronchodilators • Inhaled corticosteroids if significant symptoms and lung function response • Pulmonary rehabilitation
IIB: Moderate COPD	• Regular treatment with one or more bronchodilators • Inhaled corticosteroids if significant symptoms and lung function response or if repeated exacerbations • Pulmonary rehabilitation
III: Severe COPD	• Regular treatment with one or more bronchodilators • Inhaled corticosteroids if significant symptoms and lung function response or if repeated exacerbations • Pulmonary rehabilitation • Long-term oxygen therapy if respiratory failure • Consider surgical treatments

THE FUTURE – POTENTIAL NEW TREATMENT

With a better understanding of the cellular and molecular mechanisms involved in COPD, new molecular targets become available for the development of drugs. There are several classes of new drugs that are being developed, and could potentially be the new treatment for COPD in the near future.

- Mediator Antagonists – 5-lipoxygenase inhibitors, specific leukotriene B4 antagonists, specific antagonists of CXCR2 (one of the receptors on neutrophils that are activated by interleukin-8), humanized antibodies and soluble receptors that block TNF-*a*, and antioxidants
- Protease Inhibitors – Inhibitors of neutrophil elastase, matrix metalloproteinase inhibitors, human recombinant protease inhibitors, and gene therapy
- New Antiinflammatory Drugs – phosodiesterase 4 inhibitors, inhibitors of NF-*k*B, inhibitors of p38 mitogen-activated protein kinase, and interleukin-10

CONCLUSION

The state of the art of COPD is such that the disease continues to have a high prevalence, morbidity, mortality, and health care costs throughout the world. We should focus on prevention and detection with subsequent appropriate treatment of the disease. COPD remains very much under diagnosed. It is extremely important to detect the disease at an early stage before symptoms begin. So that we can prevent the disease from progressing to the point at which the patients suffer severely, and large amount of medical resources are spent. Although smoking cessation is the only strategy that may abate the relentless progression of airflow limitation, as discussed earlier, several treatment measures

are currently available that can reduce the symptoms of COPD. The view of COPD as an untreatable disease should be abandoned, and replaced by a positive approach to management with combination of these measures to improve the quality of life in symptomatic patients. With the recent advances in research and better understanding of the disease, it is a matter of time that more effective drugs and therapies will become available to relieve the sufferings of patients with COPD.

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The Bionic Man Revisited

Benjamin C. Sun, MD

1. Introduction

Cardiac transplantation is the mainstay therapy for patients with end stage congestive heart failure. Cardiac replacement therapy with the use of mechanical devices has made enormous strides in the past decade. Long term implantable Left Ventricular Devices (LVAD) are currently in use throughout the world with increasing frequency. The current accepted role for these devices is as a bridge to transplantation; however, as experience is gained with use of these devices, other applications may be feasible and desirable. Congestive heart failure (CHF) is a nationwide epidemic with a prevalence of 3 million victims' and more than 400,000 new cases per year. Severe heart failure unresponsive to even maximal medical therapy occurs in approximately 60,000 patients per year. Cardiac transplantation as treatment for CHF has been successful with a five-year survival in these patients approaching 70%, compared to 20-30% 2-year survival in patients with NYHA class 4 heart failure. However, because of a limited donor organ supply, cardiac transplantation will only treat 2300 patients in the United States this year. Approximately 30,000 patients are listed worldwide for cardiac transplantation every year, and only around 3500 cardiac transplantations are performed. Cardiac transplantation rates have reached a plateau since 1989 though older and more 'marginal' donors are being accepted. Unless society's perceptions towards organ donation radically changes, cardiac transplantation will remain an epidemiologic triviality.

Assist devices as a bridge to transplantation currently exacerbates this discrepancy, as the destination is still transplantation. Cardiac assist devices, total artificial hearts, xenotransplantation, and others will likely play important complimentary roles in the future treatment of CHF. These therapies need to be developed not only to prolong life but also to provide good quality of life, so the paradigm shift can occur and these alternative therapies become destination. Only then will we be able to make an epidemiologic impact on this epidemic.

2. Ventricular Assist Devices

Ventricular assist devices are currently used for three major indications. First, as a bridge to myocardial recovery. The assist system is implanted to decompress the injured myocardium allowing it to recover, as well as provide physiologic support for the patient during this time frame. Specific diagnoses include viral, post-partum cardiomyopathies, post cardiotomy, and reperfusion injury for cardiac allografts. As the heart recovers and sustains the circulation, the assist device may be explanted.

Cardiac transplant candidates who continue to deteriorate despite aggressive pharmacologic support can become candidates for assist support. The assist device is used as a bridge to cardiac transplantation and is explanted at the time of transplantation.

The third indication for assist systems is as an alternative to cardiac transplantation, though this use is only being defined now.

3. Total Artificial Heart

The total artificial heart has recently emerged from the laboratory to be used in a clinical trial for end stage heart failure patients who are not transplant candidates and not likely to love more than 30 days. The new pump recently introduced by ABIOMED (AbioCor) is a complex device which is has implantable controller and energy transfer conduits attached to the pumping 'heart'. Early results from the clinical arena are promising, and cautious optimism for the reemergence of this type of therapy abounds.

4. Future

Newer and smaller pumps are reaching the clinical arena and are also being developed. These include higher efficient, lower mass, more reliable, and more versatile devises. This field is leaving its infancy and maturing into a viable and desirable therapy for many forms of end stage heart failure.

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Regenerative Biology and Medicine: A Science Whose Time Has Come

Ray C.J. Chiu, MD, PhD

We are at the dawn of regenerative biology and medicine, using stem cells and progenitor cells to replace irreversibly damaged tissues and organs. In this presentation, we will illustrate this by reviewing some new discoveries in relation to myocardial regeneration, using adult stem cells derived from the bone marrow. To optimize the therapeutic strategy in using the bone marrow stromal cells (MSCs) for cardiovascular tissue repair, we studied their pathophysiological roles in myocardial infarction.

MSCs of Lewis rats were isolated and expanded using Caplan's method. They were labeled with pMFG-LacZ retrovirus-mediated reporter gene and then used for bone marrow transplantation. The MSCs were injected intravenously into isogenic recipient rats. These cells homed in to the bone marrow of the recipients. One week later, they were randomized to left coronary artery ligation (LCA) or sham operation group. The labeled MSCs were recruited from bone marrow via circulation, and migrated to the infarcted myocardial segments, but not to non-infarcted myocardia. Immuno-histochemical stains for cardiomyocyte specific *troponin I-c* were positive for some of these labeled MSCs, while others became endothelial cells and myofibroblasts. These findings indicate that MSCs can be recruited by signals from injured tissue, migrate to the damaged area where they undergo *in situ* differentiation to participate in tissue repair.

The MSCs also have unique immunologic properties as they are tolerogenic to T cells encountered. We repeated the marrow transplant experiment described above, except this time we did a xenotransplantation by using mice as donors, and rats without immunosuppression as the recipients. Amazingly the labeled mice MSCs survived in rats without evidence of rejection. Furthermore, the mice MSCs were able to be recruited to the infracted myocardium of the rat hosts, and undergo *in situ* differentiation, producing a stable mouse/rat cardiac chimera.

The clinical implications of these findings for the emerging new treatments of myocardial infarction and heart failure, which continues to be the leading cause of mortality and morbidity in developed and emerging nations, will be discussed.

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Current Concepts in the Management of Colorectal Cancer

W. Douglas Wong, M.D.

INTRODUCTION

Colorectal cancer is the fourth commonest malignancy and the second leading cause of cancer related deaths in the United States. In the year 2001, there were an estimated total of 135.400 new cases of colorectal cancer.[1] In terms of cancer deaths, this disease was estimated to account for 56,700 deaths in the United States. The lifetime risk of developing colorectal cancer for the American population is 1 in 17 (6%). When age adjusted incidence and mortality of colorectal cancer is evaluated from the SEER data from 1973-1997, a very pertinent finding is a decrease in incidence and decrease in mortality from this disease beginning at approximately 1985. The most plausible explanation for the decrease in incidence in the past two decades has been the effect of appropriate screening for this disease, with colonoscopic removal of precancerous adenomas, and thus prevention of development of colorectal cancer. The explanation for decrease in mortality is also likely related to screening, with the identification of colorectal cancers at an earlier stage, which are more amenable to cure than more advanced lesions; and secondly, improved multimodality therapies including surgery, radiation therapy and chemotherapy. This corresponds with a progressively improved 5-year survival for colorectal cancer, as evidenced by SEER data from 1974-1996, which showed an overall 5-year survival of 50% for this disease in 1974-1976, with an improvement to over 60% in 1989-1996. Colorectal cancer is a preventable disease by appropriate screening and removal of precursor lesions. Ongoing emphasis for routine screening of both average-risk and high-risk patient populations must be encouraged.

COLORECTAL CANCER RISK GROUPS

Colorectal cancer can be stratified into varying risk groups. Seventy-five percent of all colorectal cancers are sporadic, whereas approximately 25% of patients are considered at increased risk for this disease. Two well-recognized syndromes for inherited colorectal cancer are Familial Adenomatous Polyposis, which accounts for 1% of colorectal cancers, and Hereditary Nonpolyposis Colon Cancer, which accounts for approximately 5% of colorectal cancers. Patients with a family history of colorectal cancer are recognized as having an increased risk for this disease. This risk group (Familial Colon Cancer) accounts for 15-20% of colorectal cancers. Inflammatory bowel disease patients are in a high-risk category for this disease, and account for approximately 1% of colorectal cancers.[2] Data from the National Polyp Study[3] has demonstrated that a family history of adenoma is associated with an increased incidence of colorectal cancer in family members and that the incidence is identical regardless of whether the family member had an adenoma or an actual cancer.

Familial Adenomatous Polyposis is an autosomal dominant disease, with over 90% penetrance. Colorectal adenomas, which are the precursor lesions for colorectal cancers, develop in and around puberty. If untreated, colorectal cancer will develop in these patients once they reach approximately age 30. Extra-colonic tumors are prevalent, and include upper GI neoplasms, desmoids, osteomas, thyroid tumors, brain tumors, and other lesions. Hereditary Nonpolyposis Colon Cancer is also an autosomal dominant inherited disease. It demonstrates 70% penetrance, and colorectal adenomas commonly develop once the patients reach 20 years of age, with colorectal cancers occurring commonly in their 40s. Extra-colonic cancers occur in the endometrium, ovary, stomach,

genitourinary tract, small bowel and biliary tract. The Amsterdam Criteria have been proposed to identify patients with Hereditary Nonpolyposis Colon Cancer.[4] These criteria follow the 3-2-1 Rule, in which three or more relatives have HNPCC cancers, one of whom must be a first-degree relative of the other two; two or more generations are involved; and one cancer occurs under age 50. Germline mutations have been identified in these inherited colorectal cancer syndromes. In Familial Adenomatous Polyposis, the mutations occur in the APC tumor suppressor gene on chromosome 5q. In HNPCC, the mutations are in the DNA mismatch repair genes (MMR) on chromosomes 2, 3, 7.

PATHOLOGY OF COLORECTAL CARCINOMA

The adenoma to carcinoma pathway is now well recognized and accepted as the explanation as to how colorectal cancers develop. The pathologic aspects of colorectal carcinoma have been well recognized with established molecular correlations, in which normal mucosa progresses to development of an adenomatous polyp, which in some cases can progress to an adenoma with low-grade dysplasia, which can in turn progress to high-grade dysplasia and eventual invasive adenocarcinoma. These morphologic changes can be correlated with genetic abnormalities. An APC mutation causes normal mucosa to progress to an early adenoma with low-grade dysplasia. A subsequent K-ras mutation correlates with the progression of an early adenoma to an intermediate adenoma with low-grade dysplasia, with a subsequent DCC mutation which promotes progression to a late adenoma with high-grade dysplasia, and then finally a p53 mutation that results in an invasive adenocarcinoma. Much work is currently being undertaken to try to identify the steps in progression of a colorectal carcinoma, from an invasive adenocarcinoma confined to the bowel wall to one that develops lymph node metastasis and/or distant metastatic disease. In general, this is felt to be sequential, from the primary lesion to lymph nodes to distant organs and systemic disease. Various additional genetic abnormalities associated with this progression, such as 13q and 14q losses, and p16 gene abnormalities, have been identified. Other factors include growth factors and their receptors, collagenases and collagenase inhibitors, cell adhesion molecules, and angiogenesis mediators. There are significant prognostic implications of selected gene abnormalities, and clearly the goal is to identify predictors of recurrence in order to help target therapy. Genetic abnormalities that have been identified and are currently undergoing extensive research are transforming growth factor β1 (TGF-β1) expression,[5] p53 abnormal expression,[6,7] microsatellite instability (replication error phenotype),[8,9] and DCC gene mutation (18q loss).[10]

SURGICAL MANAGEMENT OF COLORECTAL CANCER

The extent of resection for colon cancer is based on the location and the lymphatic drainage of that section of colon. For cecal, ascending colon and hepatic flexure carcinomas, a right hemicolectomy is performed. For mid-transverse colon lesions, an extended right hemicolectomy is performed. For splenic flexure carcinomas, a left hemicolectomy is performed. For descending colon and sigmoid carcinomas, an anterior resection is performed. There has been recent interest in sentinel lymph node mapping, similar to that used for breast carcinoma and melanoma staging. Its applicability for colorectal cancers, however, is not yet justified, as there is no evidence that it actually changes current management. The technique involves injection of a blue dye in close proximity to the primary lesion, then waiting a short time to identify dye deposition in a sentinel lymph node. Studies have demonstrated that a sentinel node can be identified, and that micrometastatic disease can be identified by immunohistochemical staining. However, there has not been any definitive demonstration that patients with micrometastatic disease in the lymph nodes have a different outcome than those patients who do not have micrometastasis. A study by Bilchik et al[11] reported that 1-3 sentinel nodes were

identified in each patient. No non-sentinel node was positive if all sentinel nodes in the same specimen were negative by histopathology. Immunohistochemistry identified occult metastases in 53% of patients whose sentinel nodes were negative by conventional staging techniques. However, the significance of lymph node micrometastasis in colorectal cancer remains debatable.[12] The proponents of sentinel lymph node mapping for colon cancer maintain that a more limited resection might be feasible if the sentinel lymph node is found to be negative. At the present time this modality is experimental, and does not alter the surgical management of colon cancer.

Minimally invasive surgery for colorectal cancer is currently being extensively evaluated. Several retrospective and prospective cohort studies have demonstrated comparability of the extent of resection for colon cancer when comparing laparoscopic assisted techniques to standard open colectomy.[13,14] Some studies suggest an earlier postoperative recovery and shorter hospital stay, despite a longer operating time. The results of several multicenter randomized prospective controlled trials are being awaited, to establish whether the long-term oncologic outcome is comparable. In the NIH multicenter randomized controlled trial being conducted here in the United States, an accrual of 900 patients has been completed, and it is anticipated that in two years the survival and the recurrence data will be available. A recent quality of life assessment of this NIH trial has been published[15] showing only a very minimal short-term quality of life benefit with laparoscopic assisted colectomy, compared to standard colectomy, at two weeks postoperatively. The authors concluded that laparoscopic colon resection should not be offered to patients with colon cancer until the results of randomized controlled trials establish safety and efficacy.

Conventional surgery for rectal cancer has been evolving, based on the known extent of lymphatic spread from a primary rectal cancer. Total mesorectal excision has become the standard of care for mid- and distal rectal cancers, using a sharp dissection technique to preserve the visceral fascial envelope, thus incorporating all the regional areas of potential lymphatic spread within the mesorectum. Radial or circumferential margins have been demonstrated to be of utmost importance in minimizing local recurrence, as opposed to emphasis on distal rectal margins in years gone by. Furthermore, the surgeon has been documented to be an independent prognostic factor on multivariate analysis in several studies evaluating the outcome following rectal cancer surgery. Sphincter-saving procedures can be performed on the majority of patients with rectal cancer, with various techniques for rectal reconstruction. The simplest of the sphincter-saving procedures is a local excision, in which a full-thickness disk of the rectal wall is excised, incorporating the rectal cancer. This operation addresses only the primary lesion, and does not address the potential for lymph node metastasis. Therefore, preoperative staging is extremely important in order to accurately select patients who are best suited to local excision. Current data would suggest that the ideal candidates for local excision are T1, well-to-moderately differentiated rectal cancers within 8 cm of the anal verge, measuring less than 3 cm in diameter, in which there are no adverse histologic features. The adequacy of local excision for rectal cancer has been reexamined by two recent reports from the University of Minnesota. The recurrence rate analysis for T1 and T2 cancers resected locally with 54-month follow-up indicated that the local recurrence rate for T1 lesions was 18%, and 37% for T2 lesions. Survival rate for T1 lesions was 98%, and 89% for T2 lesions.[16] A subsequent report[17] compared recurrence and survival outcomes of patients treated with local excision and radical surgery. The 5-year local recurrence rate after local excision was 28%, compared to 4% after radical resection; and the estimated 5-year survival after local excision was 69%, compared to 82% after radical surgery. This was statistically significant for T2 lesions. These two reports raise significant concerns regarding the use of local excision as curative therapy for early rectal cancer, and the role of local excision is currently being reevaluated. A study from Memorial Sloan-Kettering Cancer Center[18] shows a similar high local recurrence rate after

local excision, and documents that the addition of adjuvant chemoradiation does not prevent such local recurrence. Furthermore, only 25% of patients were salvaged by surgery for their recurrent disease.

Sphincter-saving radical procedures using a coloanal anastomosis have been demonstrated to be oncologically comparable to the gold standard of abdominoperineal resection.[19,20] Autonomic nerve preservation surgery is inherent in the total mesorectal excision technique, and sexual function can be preserved in close to 90% of male patients under age 60.[21]

Surgery for the hereditary forms of colorectal cancer differs in the extent of resection and the timing of surgery. For Familial Adenomatous Polyposis, the impact of surveillance and surgery on survival has been well documented.[22] Recognized family members should undergo screening beginning at about age 10, and once the diagnosis of FAP is established in a given family member, prophylactic colectomy is recommended. Selected patients can be managed by a total colectomy with ileorectal anastomosis, followed by careful surveillance of the retained rectum. Other patients are best managed by a total proctocolectomy with ileoanal pouch reconstructive procedure. For Hereditary Nonpolyposis Colorectal Cancer, the overall risk of cancers of the colon and rectum approaches 80%. When an initial colorectal cancer is diagnosed in an HNPCC family member, a subtotal colectomy is the recommended procedure of choice. In female patients consideration should be given for a prophylactic hysterectomy, because of the high incidence of endometrial cancer.[23,24]

ADJUVANT THERAPY FOR COLON CANCER

Adjuvant chemotherapy for Stage III colon cancer is well established, with evidence for an overall survival benefit in node-positive patients. There are several ongoing development strategies for adjuvant chemotherapy for colon cancer. In general, adjuvant treatment follows definitive surgery, and is given with curative intent. The first successful adjuvant regime that led to the use of postoperative chemotherapy in Stage III colon cancer patients was based on a study of 929 patients with Stage III colon cancer, randomized to postoperative chemotherapy vs. observation alone. The chemotherapy used was 5FU/levamisole. Five-year disease-free survival of 61% vs. 44% ($p<.0001$) was reported.[25] Current development strategy is ongoing to identify new agents and to establish activity initially in Stage IV metastatic disease. Once it is established that a single agent has activity, then active combinations of drugs will be developed and validated in randomized trials, with the intent of moving active combinations into the adjuvant setting for Stage III disease in the hope of increasing cure rates. One example of this strategy has been the use of irinotecan (CPT-11) in colorectal cancer. This drug was found to have 17-32% response in previously untreated patients, and a 13-23% response in 5FU refractory patients. A Phase 3 randomized trial of metastatic colorectal cancer by Saltz et al[26] studied patients randomized to CPT-11 alone vs. CPT-11 with 5FU/leucovorin vs. 5FU/leucovorin alone. The triple-drug combination demonstrated a significantly improved response: 39% vs. 21%, with a statistically significant increase in survival in the Stage IV patients.[27]

Recent technological advances, along with the discovery of the role of growth factors in modulating cell proliferation and differentiation, have led to the development of new therapeutic agents for the treatment of cancer, targeting a patient population that may benefit from anti-receptor specific therapy. One such example is the development of C225 (cetuximab), which is a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFr). This antibody has been demonstrated to have cytostatic activity in preclinical studies. In a study in CPT-11 refractory patients who are found to be EGFr-positive, a 17% major response rate was documented when C225 was added to CPT-11 therapy.

ADJUVANT THERAPY FOR RECTAL CANCER

Adjuvant therapy for rectal cancer is given to improve local control and overall survival, to enhance sphincter preservation and function, and to improve quality of life. There have been five randomized trials evaluating postoperative chemoradiation for T3N0 or node-positive rectal cancer, documenting an improvement in local recurrence and in overall survival compared to surgery alone. Whether adjuvant chemoradiation for rectal cancer should be given preoperatively or postoperatively remains somewhat controversial, although there is a trend towards using the therapy preoperatively, for a number of reasons. The potential advantages of using preoperative therapy are biological, with decreased potential for seeding and increased radiosensitivity. There is also evidence to substantiate that the use of preoperative therapy can enhance sphincter preservation surgery and increase resectability of locally advanced cancers. Furthermore, there appears to be a decreased potential for acute side effects with the use of preoperative adjuvant therapy, compared to using it postoperatively. Approximately 10% of patients who undergo preoperative chemoradiation will sustain a complete pathologic response. However, the data from Memorial Sloan-Kettering indicates that it is very difficult to determine this clinically prior to surgery, and that in patients who appeared to have a complete clinical response, some 70% still had microscopic residual disease. Hence, the recommendation for radical surgery following preoperative chemoradiation is still the therapy of choice.[28] Future studies will determine the potential predictive ability of markers for the response to adjuvant chemoradiation for rectal cancer. These potential markers include thymidylate synthase, p53, Ki67, microsatellite instability, bcl-2, and DCC. Currently, results are conflicting as to the predictive capability of these markers. New chemotherapeutic agents in rectal cancer include CPT-11, oxaliplatin, UFT, tolmudex , capecitabine, and targeting agents including C225 and anti-VEGF, as well as antibodies such as 17-1a.

PREOPERATIVE STAGING OF RECTAL CANCER

The preoperative staging of rectal cancer with currently available modalities is very important in selecting optimal treatment.[29,30] The rationale for preoperative staging is to maximize cure, to minimize mortality and morbidity by perhaps selecting less radical surgical procedures, and to allow participation in controlled trials where preoperative staging allows comparable comparison of treatment regimens for similarly staged tumors. The underlying assumption is that treatment will vary with stage of disease. Preoperative staging of rectal cancer is performed to try to identify the early confined lesion, for which local therapy may be appropriate; and, at the other extreme, to identify the locally advanced lesion, which may benefit from preoperative adjuvant chemoradiation. The modalities that we have available are clinical assessment, endorectal ultrasound, CT imaging and MRI imaging. CT scanning is useful for identification of distant metastatic disease, but it does not show the layers of the rectal wall, nor is it reliable for determining lymph node metastases. Conventional MRI is comparable to CT scanning; however, the endorectal MRI coil does allow visualization of the layers of the rectal wall, and is comparable to endorectal ultrasound in depth of wall staging. Endorectal ultrasound imaging is the simplest and most accurate modality for staging depth of wall invasion. It can be used in the clinic setting, and is of value as an extension of the physical examination. In a comparative systematic review of articles evaluating the efficacy of staging modalities for rectal cancer,[31] identified endorectal ultrasound as the most accurate at detecting bowel wall penetration, with an overall accuracy of 87%, compared to 84% for MRI with endorectal coil, and 82% and 73% respectively for conventional MRI and CT scanning. However, for detecting lymph node status endorectal ultrasound accuracy was only 74%; whereas MRI with endorectal coil was the best at 82%.

Endorectal ultrasound imaging is the simplest and most accessible staging modality, and is the current procedure of choice for the preoperative staging of rectal cancer.

SCREENING AND PREVENTION

The prevention of colorectal cancer is an achievable goal. Screening for colorectal cancer and adenomatous polyps should be offered to all men and women without risk factors beginning at age 50. Furthermore, patients identified with increased risk for this disease should undergo appropriate screening on a regular basis. For patients with a family history of colorectal cancer or adenoma, screening is recommended beginning at age 40 or 10 years before the age of diagnosis of the family member with this disease. Currently recommended screening modalities include annual fecal occult blood testing with flexible sigmoidoscopy every five years, or colonoscopy every five years or double contrast barium enema with proctoscopy or flexible sigmoidoscopy every five years. Colonoscopy is the screening method of choice in many centers today and is the preferred method for patients at increased risk for this disease. Mortality reduction from various forms of colorectal screening is well established. Fecal occult blood testing on a yearly basis has been shown to reduce mortality from this disease by 33%. Flexible sigmoidoscopy on an every-five-year basis has been demonstrated to reduce mortality by 30%. The estimated combined mortality reduction with these two modalities is in the vicinity of 50%.[32] The National Polyp Study[33] demonstrated a significant decrease in the incidence of colorectal cancer following colonoscopic polypectomy. There is increasing data to suggest that, for patients in the average-risk category, an initial colonoscopy followed by no further surveillance results in a cumulative incidence of colorectal cancer identical to that of initial colonoscopy followed by regular surveillance colonoscopy. Both of these options show a significantly diminished incidence of colorectal cancer, compared to the non-screened population. This has led to a proposal for the average risk population of a once-in-a-lifetime screening colonoscopy, in which a colonoscopy negative for any adenoma results in no further screening for that individual. If a patient is found to have an adenoma, then surveillance colonoscopy after removal is recommended. Virtual colonoscopy is a new modality that uses CT scan colography to evaluate the colon for polyps or neoplasms. This modality shows considerable promise as a screening tool for colorectal neoplasms. The data to date suggests that the detection of colorectal polyps and cancer by helical CT with 3-dimensional reconstruction approaches that of conventional colonoscopy and exceeds that of double-contrast barium enema.[34] In a prospective study in which 100 patients at high risk for colorectal neoplasm underwent virtual colonoscopy followed by immediate conventional colonoscopy, the authors concluded that both modalities had a similar efficacy in the detection of polyps 6 mm or more in diameter.[35] The advantage of conventional colonoscopy is that this can be completed as a one-stage procedure, and polyps can be removed if they are found. However, the advantage of virtual colonoscopy is that it is a less invasive procedure, and in instances where a stenotic lesion precludes completion of conventional colonoscopy, or colonic anatomy limits a complete exam, virtual colonoscopy can be very efficacious.

The future approach to colorectal cancer prevention will be with the use of genetic testing to identify which patients are at risk of developing polyps and eventual cancers. Currently, patients identified as having a hereditary form of colorectal cancer are counseled with respect to the potential value of genetic testing to identify a mutation. If the mutation can be identified it has value in determining the risk of other family members for developing this disease.

Colorectal cancer is a preventable disease, and every effort should be made to encourage routine screening of the average-risk population, as well as those with an increased risk for this disease.

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Assisted Reproductive Technology

Pak Chung, M.D.

(The following are Power Point slides of Dr. Chung's presentation)

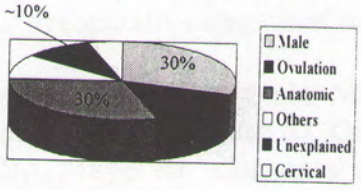
Fertility Basics

EGG + SPERM + ANATOMY = PREGNANCY

Definition of Infertility

- Traditionally defined as inability to conceive after one year's unprotected intercourse
- Affects 10-15% of couples of all ethnic background
- Monthly fecundity rate (young couple):
  ~20%
- After one year of trying:
  ~3-5%

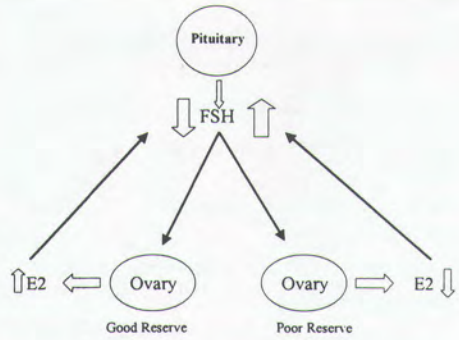
Etiologies of Infertility



Infertility Re-defined

- Most ...cal determi... ...gnanc... FEM...
- Ol... wo...n dese... more expeditiou... ...and tr... men... n

AGE



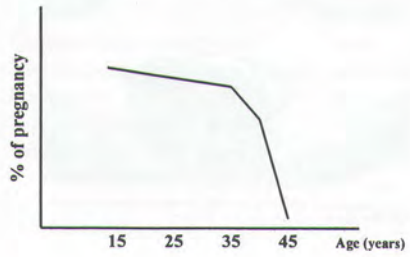
Evaluation of Ovarian Reserve

- ***Day 3 FSH, Estradiol leve ls***
- Clomiphene citrate challenge test

Assisted Reproductive Technology

- In vitro fertilization (IVF)
- Gamete intrafallopian transfer (GIFT)
- Zygote intrafallopian transfer (ZIFT)
- Micromanipulation techniques
  - Intracytoplasmic sperm injection (ICSI)
  - Assisted hatching
  - Preimplantation genetic diagnosis (PGD)
- Cryopreservation of gametes and embryos
- Epididymal/testicular sperm retrieval
- Donor oocytes/sperm/embryos
- Gestational surrogacy

The Impact of Female's Age



Assisted Reproductive Technology

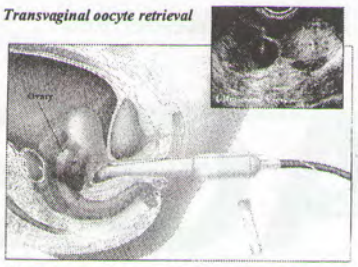
Indications (IVF)

1. Tubal factor
2. Age of female
3. Endometriosis
4. Severe male factor
5. Failed other treatments
6. Idiopathic infertility
7. Genetic defects
8. Others

Medications in IVF Stimulation

- Gonadotropin releasing hormone analog
  (prevents ovulation)
- Gonadotropins
  (FSH: urine-derived/recombinant
  HMG: urine-derived)
- Gonadotropin releasing hormone antagonist
  (prevents ovulation)

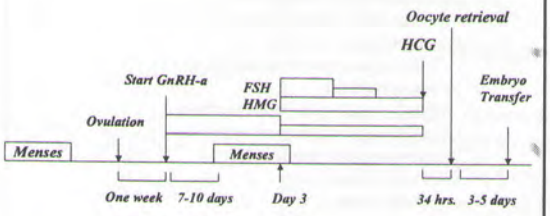
Transvaginal oocyte retrieval

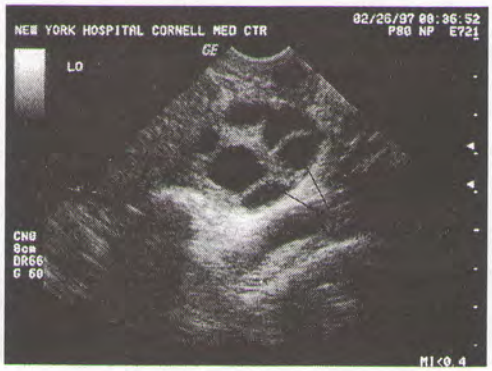


Using ultrasound to view the ovary, the physician inserts the needle through the wall of the vagina into the ovary and removes the egg for use in IVF or GIFT.

Luteal GnRH-analog Protocol

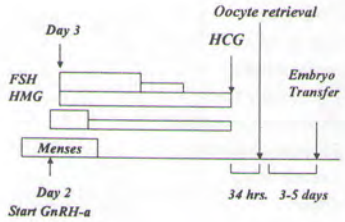
(Young patients with normal ovarian reserve)



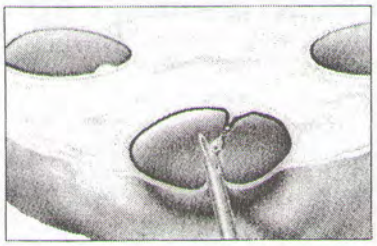


Flare/No GnRH-a Protocol

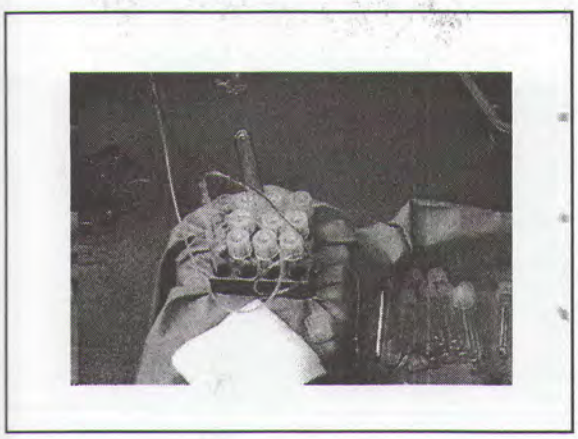
(Anticipated poor responders)

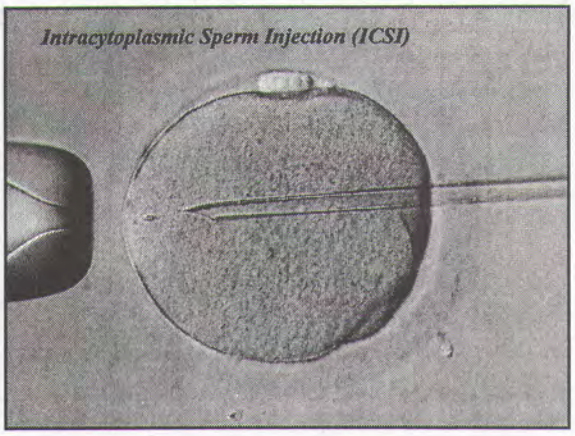


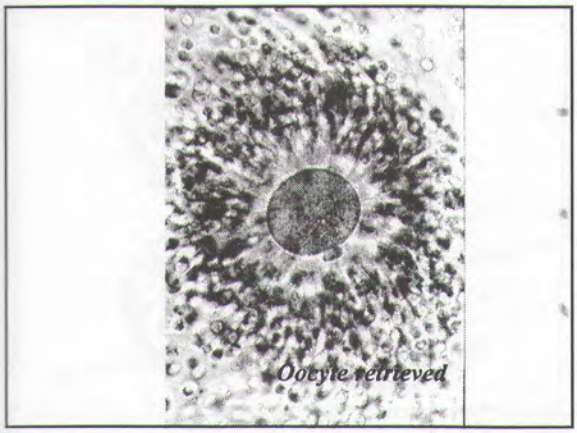
Transvaginal Oocyte Retrieval Procedure

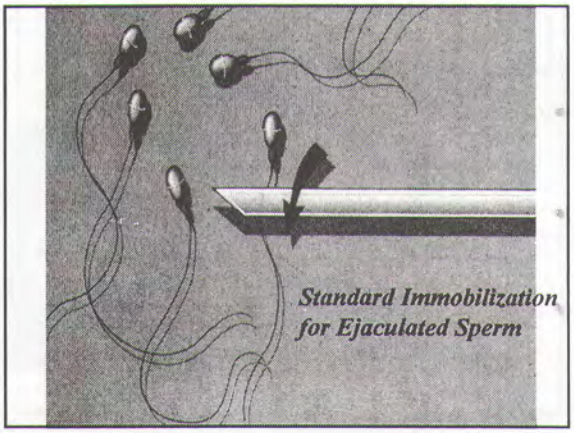


Hormones may be administered to the woman to produce multiple eggs. The eggs are then retrieved from the ovary.



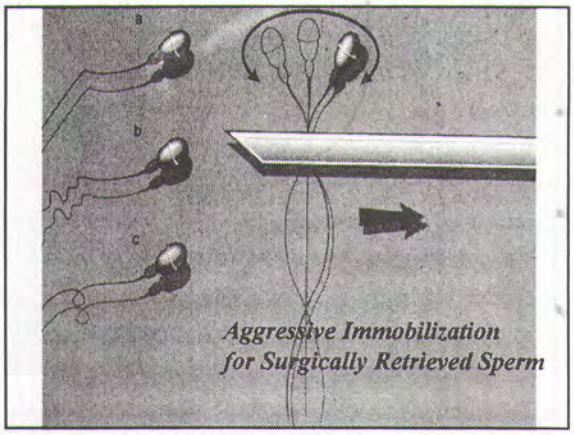


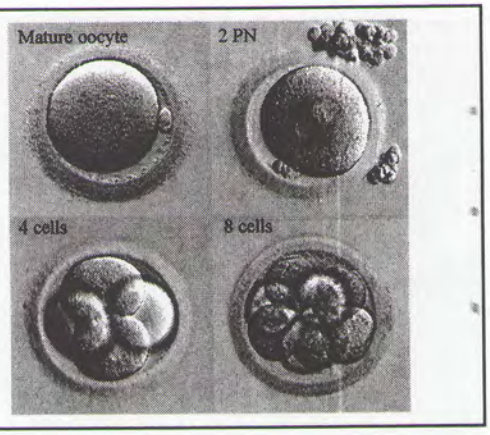


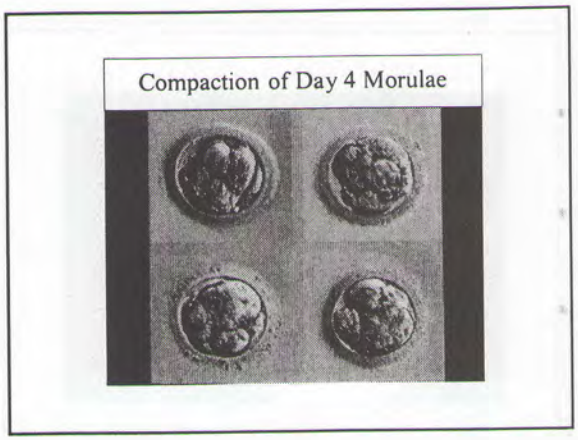


Types of Sperm & Methods of Fertilzation

• Ejaculated sperm (fresh, frozen)	*Insem./ ICSI*
• Electroejaculated sperm (fresh, frozen)	*Insem./ICSI*
• Donor sperm	*Insem./ICSI*
• Epididymal sperm (fresh, frozen)	*ICSI*
• Testicular sperm (fresh, frozen)	*ICSI*

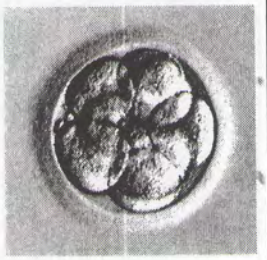


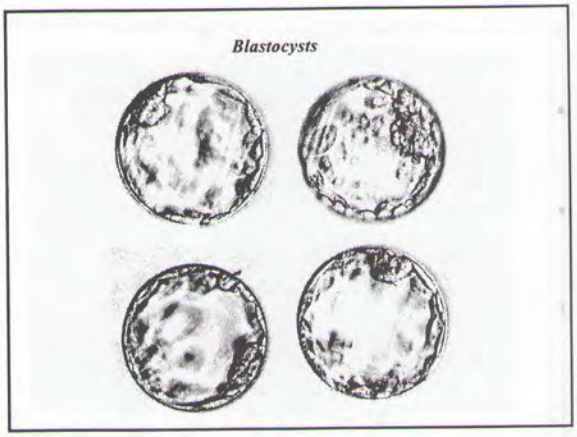




Good Implantation Potential

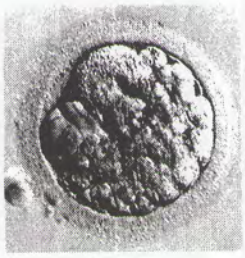
- Acceptable cleavage rate for Day 3
- Regular-sized blastomeres
- Few or no cytoplasmic fragments

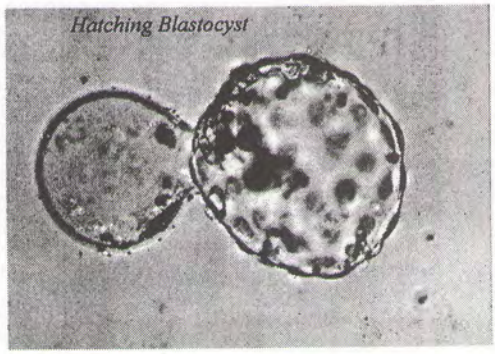




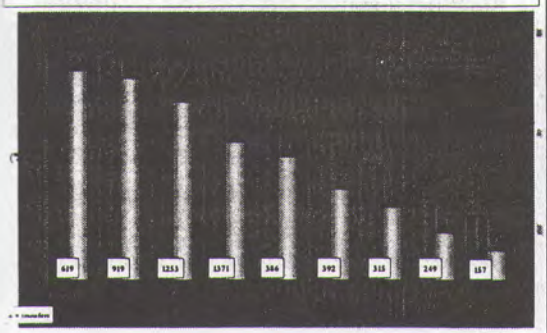
Poor Implantation Potential

- Severe cytoplasmic fragmentation
- Acytoplasmic fragments
- Retarded growth





Pregnancy Outcome by Age

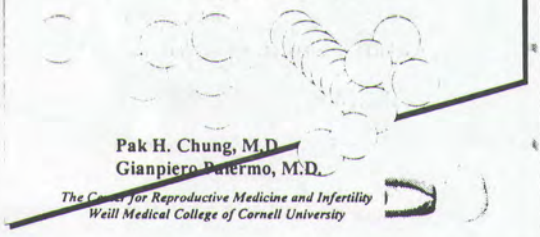


When Do We Need ICSI ?

Sperm Indications

- <500,000 motile spermatozoa
- <1% normal forms
- Abnormal acrosome
- Antisperm antibodies
- Compromised motility
- Cryptozoospermia
- Azoospermia
- Fertilization failure

Seven Years of ICSI At Cornell



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When Do We Need ICSI ?

Oocyte Indications

- Too few oocytes
- Excessive thickness of the zona pellucida
- Oocyte dysmorphism
- Abnormal cortical granuli reaction

History of Treatment of Male Factor Infertility

Sperm Conc. (M/cc)	Treatment
20 - 200	Normal
10 - 20	IUI
2 - 10	IVF
<2	IVF with *ICSI*

Types of Sperm for ICSI

- Ejaculated sperm (fresh, frozen)
- Electroejaculated sperm (fresh, frozen)
- Donor sperm
- Epididymal sperm (fresh, frozen)
- Testicular sperm (fresh, frozen)

ICSI Results at Cornell
(September 1993 – September 2000)

Spermatozoa	Cycles
Ejaculated	4,446
Surgically retrieved	634
Total	5,080

Semen Origin and ICSI Outcome

Semen origin	Cycles	Fertilization (%)	Clinical pregnancies (%)
Fresh ejaculate	4,179	26,492/34,996 (75.7)*	1,783 (42.7)†
Frozen ejaculate	317	1,448/2,012 (72.0)*	101 (46.5)†
Electroejaculate	33	264/327 (80.7)*	16 (48.5)†
Frozen electroejaculate	9	47/75 (62.7)*	5 (55.6)†
Retrograde ejaculate	8	76/90 (84.4)*	3 (37.5)†

*χ^2 test, 5x2, 4 *df*, Effect of semen origin on fertilization rate, $P = 0.0001$
†χ^2 test, 5x2, 4 *df*, Effect of semen origin on clinical pregnancy rate, $P < 0.01$

ICSI with Ejaculated Spermatozoa

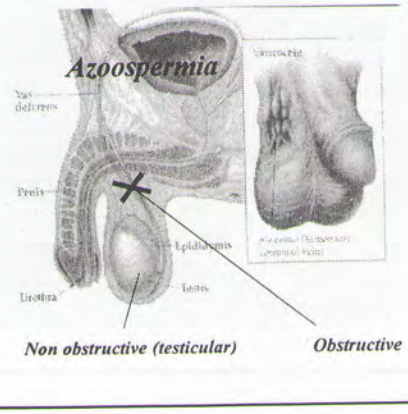
Cycles	4,446
Mean maternal age (± SD)	36.2 ± 5
Normal semen parameters*	460
Abnormal semen parameters	3,986

*(WHO; de Kretser; Kruger)

Efficacy of ICSI in the Different Categories of Azoospermia

Survival and Fertilization Characteristics
(Ejaculated Spermatozoa)

MII oocytes injected	37,500
Oocytes that survived (%)	35,233 (94.0)
Oocytes with 2PN	28,327 (75.5)
1PN	1,183 (3.2)
3PN	1,486 (4.0)



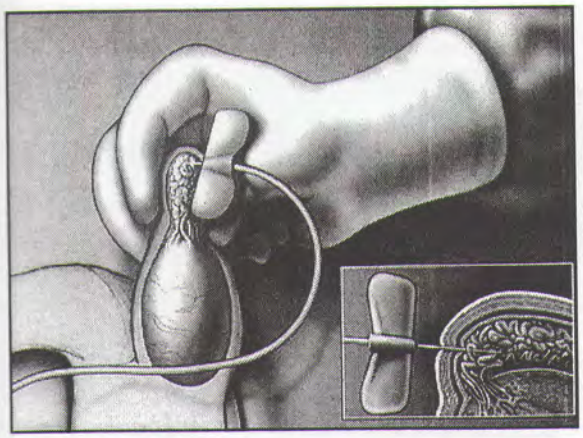
ICSI in Azoospermic Patients

Cycles	634
Maternal age (M ± SD)	34.4 ± 5
Epididymal spermatozoa	381
Testicular spermatozoa	253

ICSI Outcome
(Epididymal Spermatozoa)

	Sperm	
	Fresh	Frozen/Thawed
Cycles	172	209
Density (x 10^6/ml ± SD)	28.7 ± 41	23.0 ± 28
Motility (M ± SD)	18.4 ± 17*	3.3 ± 7*
Morphology (M ± SD)	1.8 ± 3	1.1 ± 2
Fertilization (%)	1,348/1,819 (74.1)	1,376/1,890 (72.8)
Clinical pregnancies (%)	114 (66.3)†	91 (43.5)†

*Student's *t*-test, two independent samples: Effect of cryopreservation on sperm motility, $P < 0.0001$
†χ^2, 2×2, 1 *df*, Effect of cryopreservation on clinical pregnancy rate, $P = 0.0001$



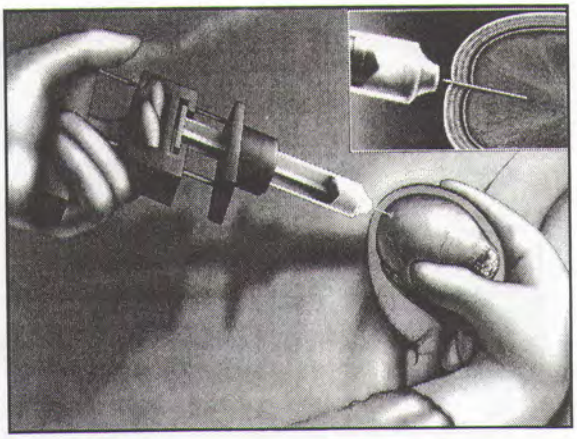
Indications for Surgical Sperm Retrieval from Testes

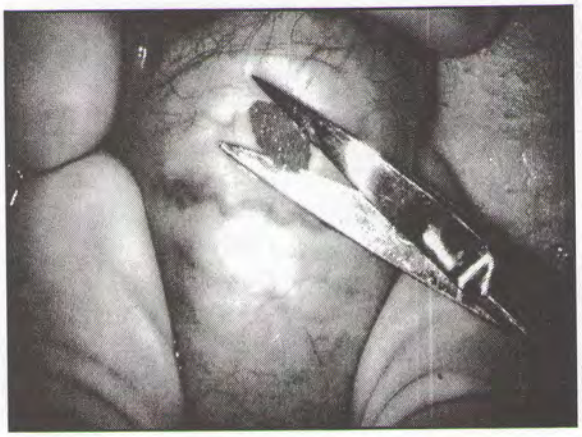
Non-obstructive azoospermia: TESE

- **Hypospermatogenesis**
- **Maturation arrest**
- **Sertoli cell only (germ cell aplasia)**

ICSI Outcome
(Epididymal Spermatozoa)

	Obstruction	
	Congenital	Acquired
Cycles	219	162
Density (x 10^6/ml ± SD)	29.1 ± 40	20.7 ± 24
Motility (M ± SD)	10.4 ± 14	9.8 ± 15
Morphology (M ± SD)	1.7 ± 2	1.1 ± 2
Fertilization (%)	1,658/2,270 (73.0)	1,066/1,439 (74.1)
Clinical pregnancies (%)	126 (57.5)	79 (48.8)

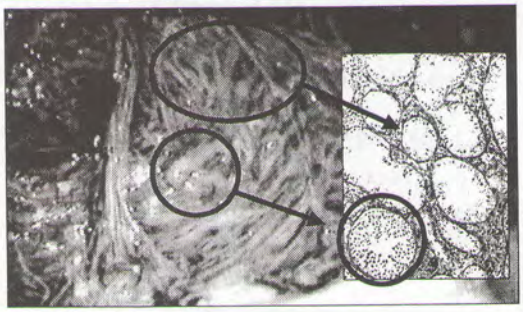




ICSI Outcome
(Testicular Spermatozoa)

	Sperm	
	Fresh	Frozen/Thawed
Cycles	208	45
Density (x 10^6/ml ± SD)	0.6 ± 3	0.1 ± 0.4
Motility (M ± SD)	6.6 ± 12	1.9 ± 5
Morphology (M ± SD)	0	0
Fertilization (%)	1,217/1,948 (62.5)	219/375 (58.4)
Clinical pregnancies (%)	94 (45.2)	17 (37.8)

Microsurgical Identification of Sperm-producing Tubules by Appearance



Genetic Basis of Male Infertility

ICSI Outcome
(Testicular Spermatozoa)

	Azoospermia	
	Obstructive	Non-obstructive
Cycles	71	180
Density (x 10^6/ml ± SD)	0.6 ± 1	0.5 ± 3
Motility (M ± SD)	6.0 ± 8	5.6 ± 12
Morphology (M ± SD)	0	0
Fertilization (%)	421/601 (70.0)*	1,015/1,722 (58.9)*
Clinical pregnancies (%)	33 (46.5)	78 (43.3)

*χ^2. 2x2. 1 *df*. Effect of etiology of azoospermia on fertilization rate. $P = 0.0001$

Chromosomal Screening

Non-obstructive Azoospermia

No. of evaluated males	270
Abnormal karyotypes	35 *(13.0%)*

Abnormal Karyotypes

Non-obstructive Azoospermia

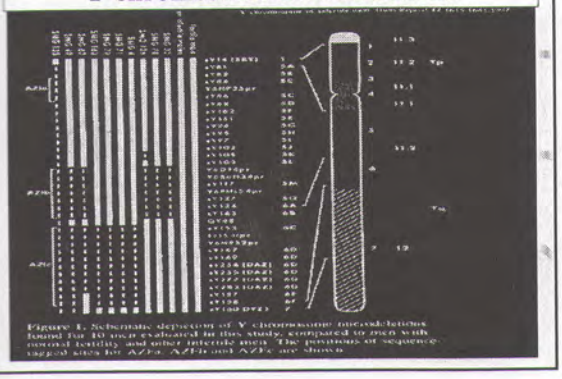
- Autosomal: 6
  - 2 - translocation
  - 3 - inversions
  - 1 - deletion
- Gonosomal: 29
  - 22 - Klinefelter's Syndrome
    - 20 - 47,XXY
    - 1 - 46,XY/47,XXY/49,XXXXY
    - 1 - 47,XXY/48,XXXX
  - 1 - 46,XY (delYq)
  - 2 - 45,X/46,XY
  - 3 - 46,XX (Sry+)
  - 1 - 46,XpsY

Klinefelter's Pregnancies

Delivered:

- 4 singletons (46,XY)
- 2 twin (46,XY 46,XX)
- 1 twin (46,XX 46,XX)

Y-chromosome microdeletions

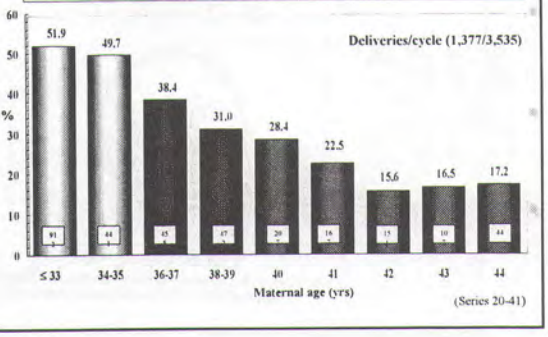


Overall Results

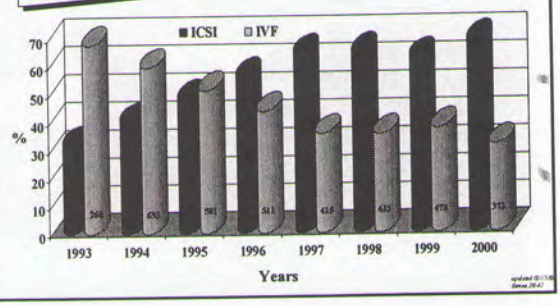
ICSI and Klinefelter's Syndrome

Cycles	16
Oocytes fertilized/injected (%)	126/201 (62.7)
Embryos replaced	51
Clinical pregnancies (%)	7 (43.8)

Effect of Maternal Age on ICSI Deliveries



Distribution of ICSI



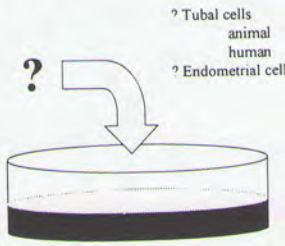
Background

- IVF pregnancy rates have been far from being 100%
- Factors contributing to failed IVF:
  - Age
  - Chromosomal abnormalities
  - Decreased endometrial receptivity
  - *Suboptimal culture conditions*

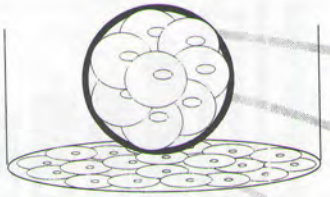
ICSI vs. IVF

No. of (%)	ICSI	IVF
Cycles	5,080	4,045
Fertilized oocytes (2PN/MII inseminated)	32,487/43,532 (74.6)	26,606/42,258 (63.0)
Transfers	4,836 (95.2)	3,708 (91.7)
Mean embryos transferred	3.3	3.5
Clinical pregnancies (FHB)	2,224 (43.8)	1,728 (42.7)

What else to add to conventional medium?



Autologous Endometrial Coculture in Human IVF



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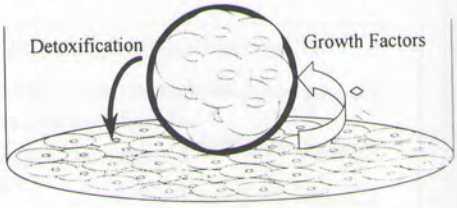
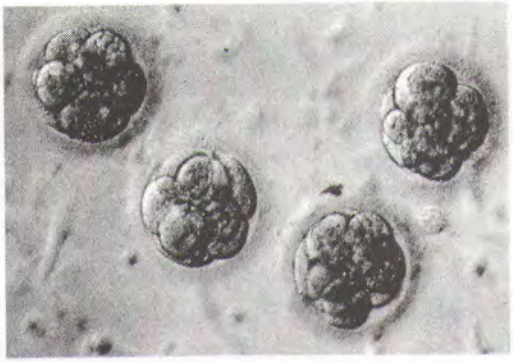
Proposed Mechanisms of Action

Background

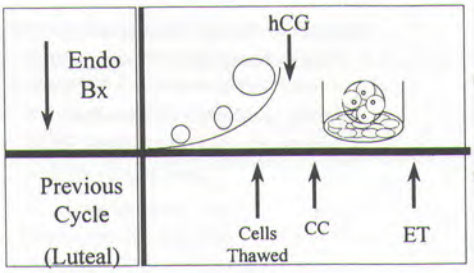


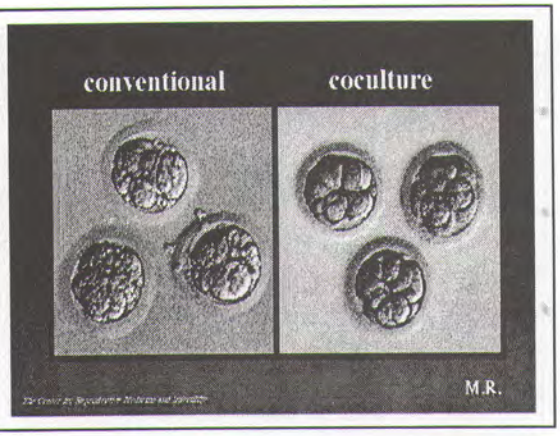
Endometrial Co-Culture

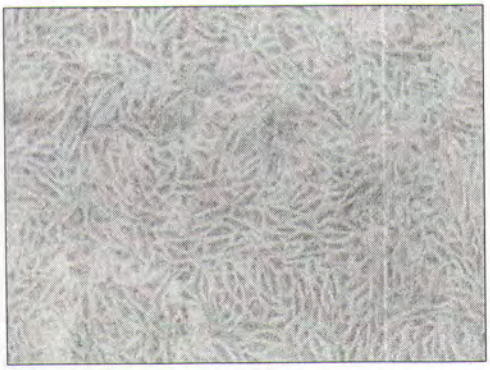
- Biopsy of the endometrial lining during mid luteal phase in a prior menstrual cycle - no permanent loss of tissues
- Cryopreservation of lining cells
- Thawing of cells around oocyte retrieval time
- Culturing the gametes and embryo in conventional medium *plus thawed endometrial cells*
- Early exposure of embryos to uterine environment



Overview







Blastocyst (Day 5) Transfer

Increasing implantation rate and
Decreasing multiple pregnancy rate

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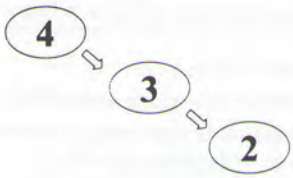
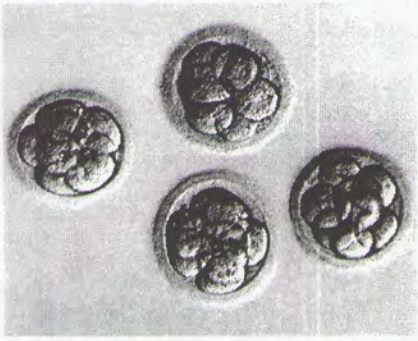
Background

- Traditional D2 or D3 embryo transfer
- Implantation rate per embryo between 5 and 30%
- Requires multiple embryo transfer

Selective Fetal Reduction



Four embryos, four babies



Why should blastocysts have a higher IR than cleavage stage embryos?

- Synchronization of uterus and blastocyst
  - D2-3 embryos reside in fallopian tubes in vivo
  - ? premature exposure of d2-3 embryos to uterine factor
- Viability assessment of blastocyst
  - genomic activation occurs around D4

High Order Multiples

- Increased risks of prenatal complications, e.g.
  - preeclampsia
  - gestational diabetes
  - placental abnormalities
  - malpresentation
  - preterm labor and deliveries
- Increased costs to care for preterm infants

Impedance to blastocyst transfer in the past

- Lack of appropriate medium in vitro to sustain viability of blastocyst
  - cultures supportive of zygote growth is inhibitory to blastocyst development
  - inability to recognize changing physiological needs of embryos during development to blastocyst stage

Sequential Culture Media
(Gardner, 94, 97; Barnes, 95)

G1	G2
– levels of CHO present in fallopian tube	– levels of CHO present in uterus
– EDTA	– amino acids
– serum albumin	– No EDTA
	– serum albumin

Blastocyst Transfer: Conclusions

- Higher IR
- Fewer to transfer
- Fewer triplets or higher order multiples
- Viability assessment- genomic activation
- New horizon for PGD- trophectoderm bx

Candidates for Blastocyst Transfer

1. Young women with good ovarian reserve
2. Older women with adequate # (≥4) of pronuclear embryos
3. Women for whom multiple pregnancy will be of risk
   - DES exposed uterus
   - uterine anomalies etc.
4. Donor oocyte recipients

PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

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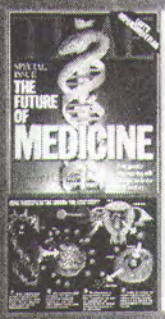
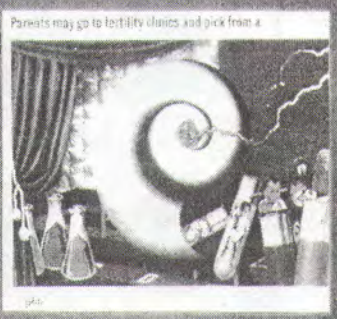
WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

Pitfalls

- Risking no transfer
- How many of the embryos which fail to reach blastocyst stage would have been able to result in pregnancies if transferred earlier?

ARE WE DESIGNING BABIES?



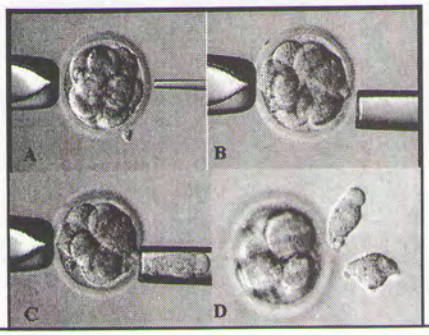


Prenatal Diagnosis (CVS, Amniocentesis)

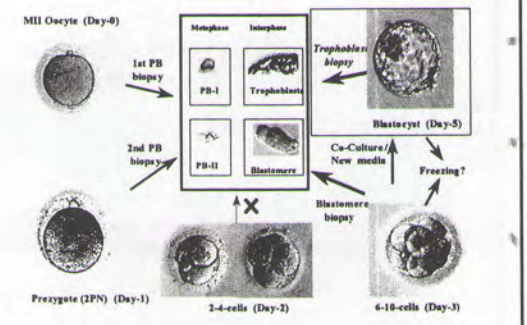
Vs.

Preimplantation Genetic Diagnosis (PGD)

DAY-3 EMBRYO BIOPSY



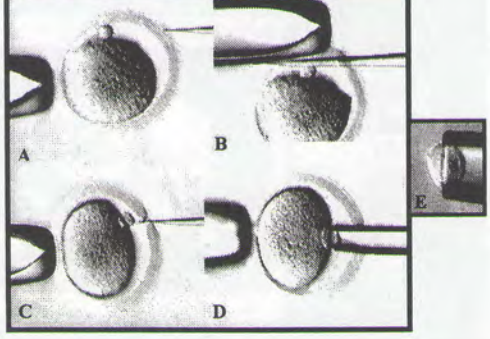
PGD



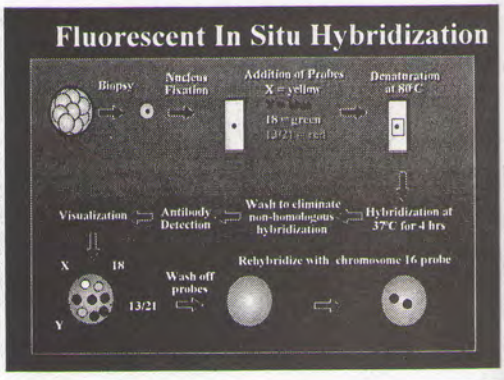
Laboratory Methods for PGD

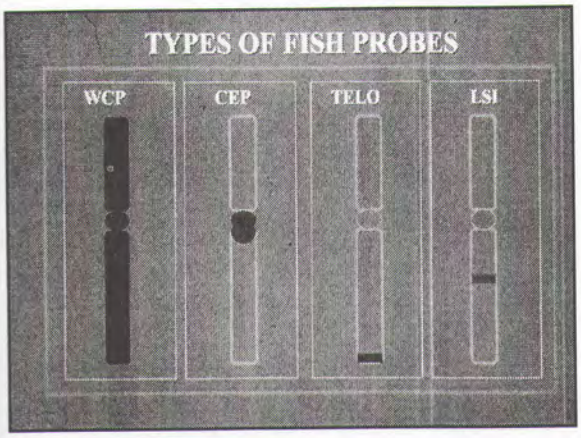
- *Fluorescent In Situ Hybridization (FISH)*
  - Sex-linked diseases
  - Numerical chromosomal disorders
  - Structural chromosomal disorders
- *PCR*
  - Single gene defects

POLAR BODY BIOPSY

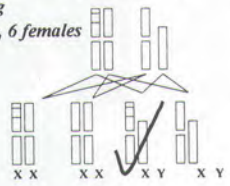


Fluorescent In Situ Hybridization

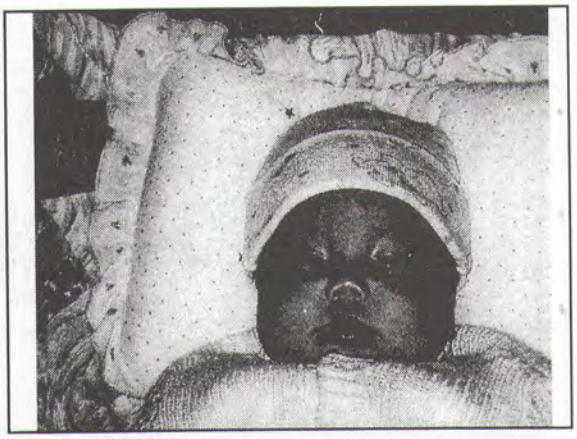




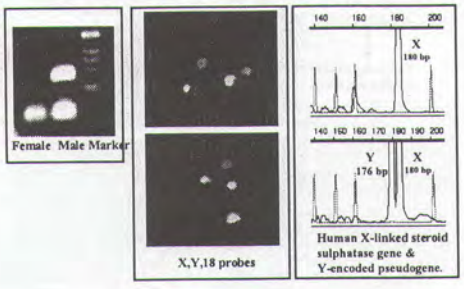
- *CC 31 year-old G2P0200*
- *Two spontaneous pregnancies:*
  - *24 weeks loss, marked hydrocephalus, fetal death in utero, male fetus*
  - *26 weeks loss, same*
- *Referred for counseling*
- *Genetic counseling discovered sex-linked hydrocephalus*
- *Underwent IVF, PGD for sexing*
- *13 oocytes, 10 embryos, 4 males, 6 females*
- *2 XX embryos replaced*



FISH - PGD FOR SEX-LINKED DISORDERS



EMBRYO SEX DETERMINATION

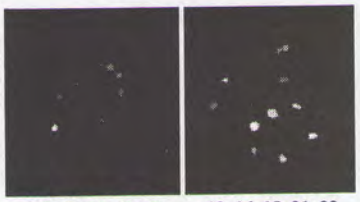


FISH - PGD FOR NUMERICAL CHROMOSOME ANALYSIS

Numerical Chromosomal Disorders:

Age- Related

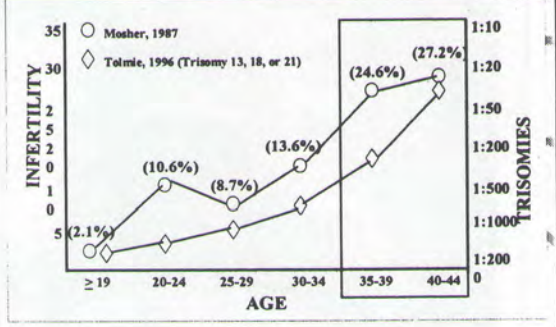
PGD FOR ANEUPLOIDY ANALYSIS



X, Y, 13, 18, 21 13, 16, 18, 21, 22

(or any 3~4 Chromosomes from 1, 2, 3, ...22, X, Y)

INFERTILITY, VIABLE TRISOMY & AGE



FISH - PGD FOR STRUCTURAL CHROMOSOME ANALYSIS

WHAT CHROMOSOMES SHOULD BE ANALYZED?

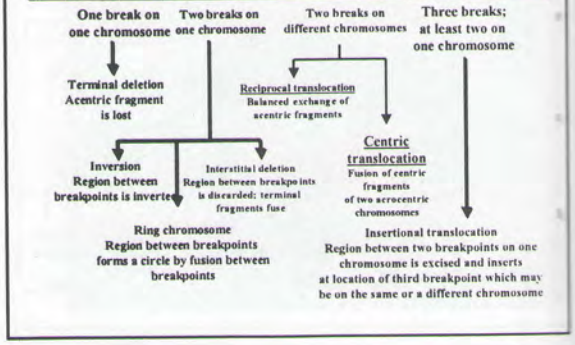
To eliminate the risk of trisomic offspring:

X, Y, 13, 18, 21

To reduce spontaneous abortions/increase implantation rate

1, 15, 16, 17, 22 (& others)

MAJOR TYPES OF STRUCTURAL CHROMOSOMAL ABNORMALITIES

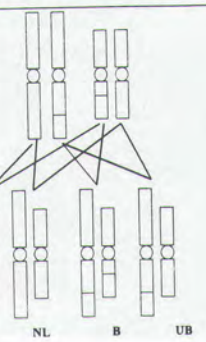


RECIPROCAL TRANSLOCATION

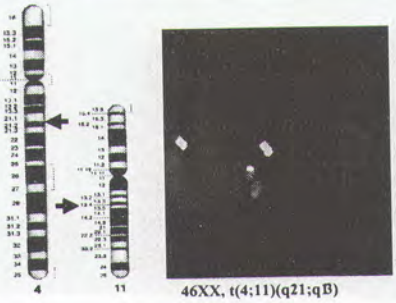
Balanced translocation:

occurs in approximately 1/500 individuals
decreases fertility and increases risk of miscarriage

27 year old G6P0060
5 first trimester miscarriages, 1 ectopic
Found to have balanced translocation of chromosomes 4 and 11
Underwent IVF
14 oocytes, 12 embryos
Polar body and blastomere biopsy
10 unbalanced, 1 balanced, 1 normal
The normal one replaced
Normal healthy infant



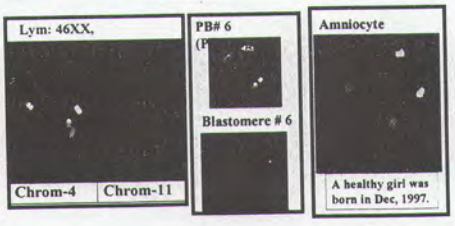
FISH for Reciprocal Translocation



PCR - PGD FOR SINGLE GENE ANALYSIS

FIRST (CRMI) CASE FOR RECIPROCAL TRANSLOCATION

- 27 year old (April, 1997, Case ID: 34-028)
  During 1/95-9/96 (21 months) five spontaneous miscarriages and 1 ectopic.



SPECIFIC DISORDERS

- Chromosomal disorders (X-linked, Trisomies, Translocations, ...)
- Connective tissue disorders (Marfan, ...)
- Hematologic disorders (Sickle cell, Thalassemias, RhD, ...)
- Mental and behavioral disorders (Autism?, Fragile X?...)
- Metabolic disorder (Tay-Sachs, ...)
- Neurologic disorders (HD, ...)
- Neuromuscular disorders (DMD, MD, SMD,...)
- Renal disorders (FA, ...)
- Respiratory system disorders (CF, ...)
- Craniofacial disorders
- Dermatologic disorders
- Endocrinologic disorders
- Gastrointestinal disorders
- Ophthamologic disorders
- Rheumatologic disorders
- Skeletal disorders

FIRST UNAFFECTED BABIES
(8-2-98, 3 month)

PGD ANALYSIS
M 1 2 3 4 5 6 7 8
361 bp
291 bp
201 bp
90 bp
74 bp
Control
Sperm

AMNIOCENTESIS
DNA
Father A
Father B
M 1 2 3 4 5 6 7
464 bp
201 bp
90 bp
74 bp

SICKLE CELL ANEMIA
DNA ANALYSIS
DNA Size Marker
Homozygous
Normal
Carrier
Affected
3
4
2
361 bp
291 bp
201 bp
200 bp
180 bp
90 bp
74 bp

EMBRYO TRANSFERRED

PGD FOR SICKLE CELL ANEMIA
Autosomal recessive (11p).
A -> T mutation causes Glu. to Val.
on the 6th codon of hemoglobin β-chain.
◊ The GAG (Glu) to GTG (Val) substitution
abolishes a restriction site (Dde I).
RFLP
A nested-PCR to amplify DNA from single cells, followed by RFLP
571 bp
Exon - 1
Exon - 2
90 bp
201 bp
74 bp
364 bp
AS, But not AC

MOST COMMON CF MUTATIONS

Mutations	Frequency (%)	Population	PGD
ΔF508	28,948 (66.0)		YES
G542X	1,062 (2.4)	Spanish	?
G551D	717 (1.6)	English	yes
N1303K	589 (1.3)	Italian	?
W1282X	536 (1.2)	Jewish-Ashkenazi	YES
R553X	322 (0.7)	German	yes
621+1G->T	315 (0.7)	French-Canadian	?
1717-1G-A	284 (0.6)	Italian	?

Also:
R117H (0.3); R1162X (0.3); R347P (0.2); 3849+10kb C->T (0.2);
ΔI057 (0.2), 18Ω-1G->A (Yes)

Data are obtained from the CF Genetic Analysis Consortium (1994).
http://www.genet.sickkids.on.ca/cftr/
Frequency is based on the screening of 43,849 CF chromosomes.
Not all of them have been tested for the indicated mutations.

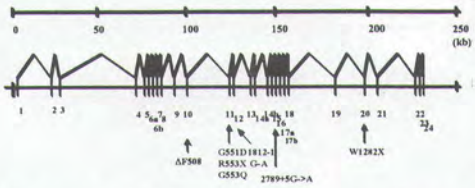
Ovarian Tissue Preservation & Transplantation: What's New?

Pak H. Chung, M.D.
Center for Reproductive Medicine & Infertility
Cornell University Weill Medical College

PGD FOR CYSTIC FIBROSIS

GENE
Chromosome 7 (q31-q32);
~250 kb, 27 exons, 1840 amino acids

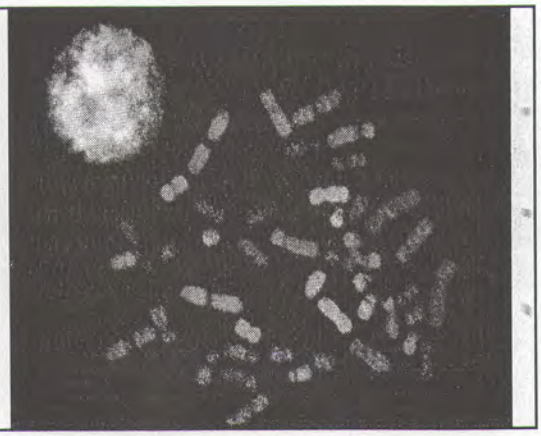
CLINCAL
Common, severe, autosome recessive;
≥ 929 mutations, + 195 seq. variation (8/00)

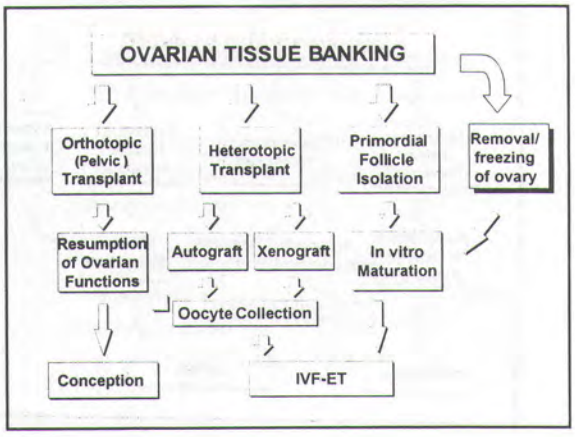


More mutations (e.g., male infertility-related) may be able diagnosed in the future.

Reproductive Preservaion Strategies

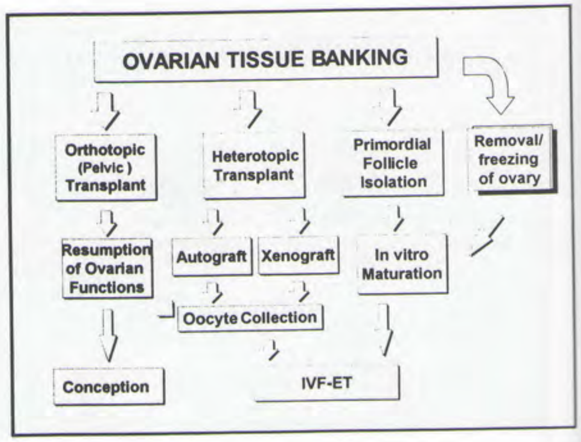
- Cryopreservation of:
  - Sperm
  - Embryo
  - Oocyte
  - Ovarian Tissue

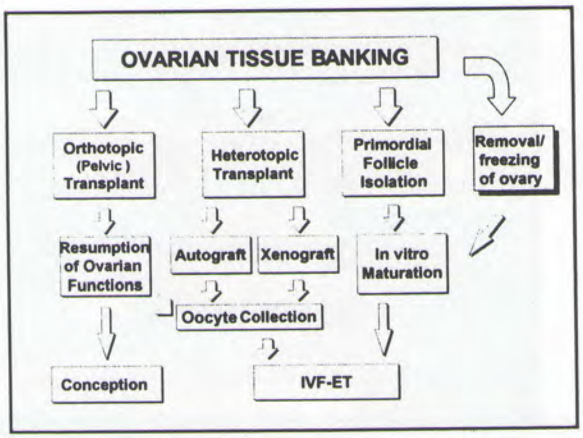


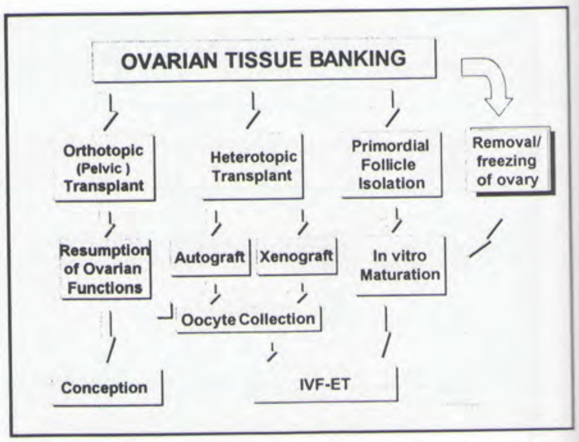


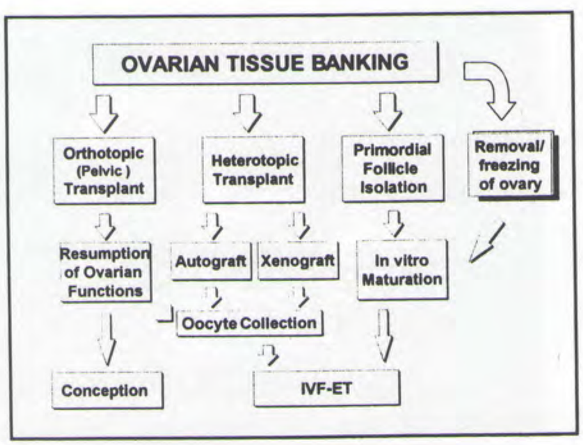
Who is a candidate for ovarian tissue banking ?

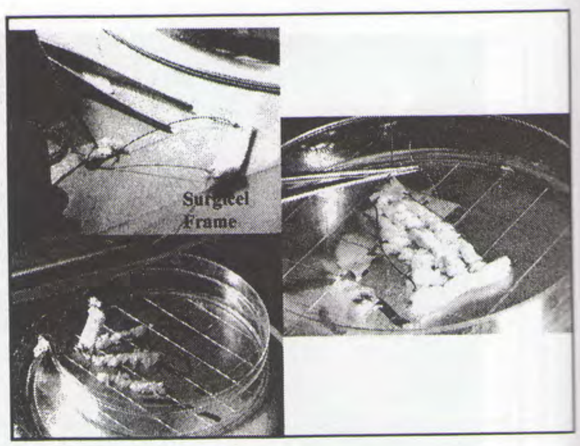
- Cancer prior to chemotherapy and or radiotherapy
  - *>4000 female children/teenagers with curable cancer*
- Bone marrow transplant
- *Single, older ?*
- *Convenience ?*

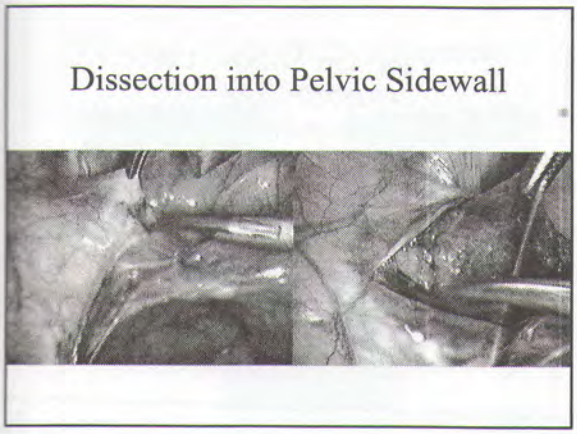


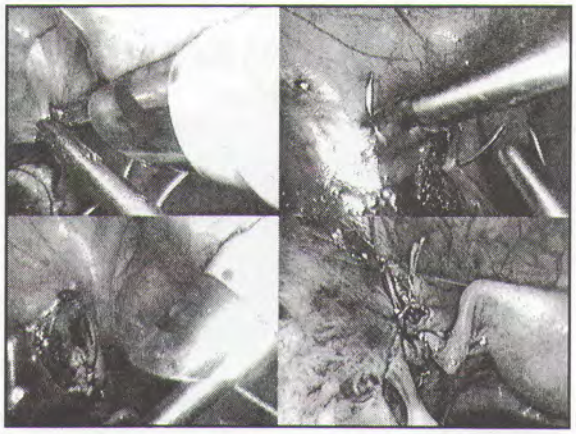


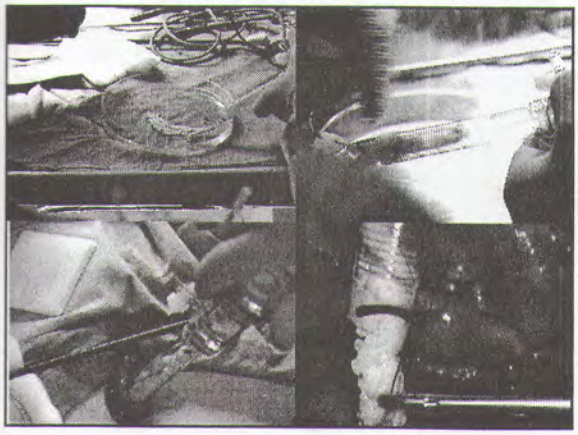


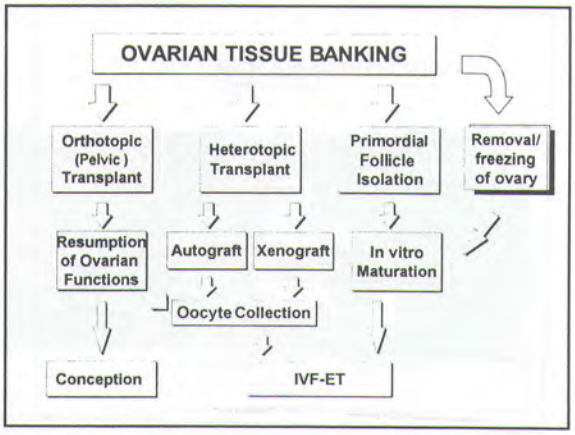


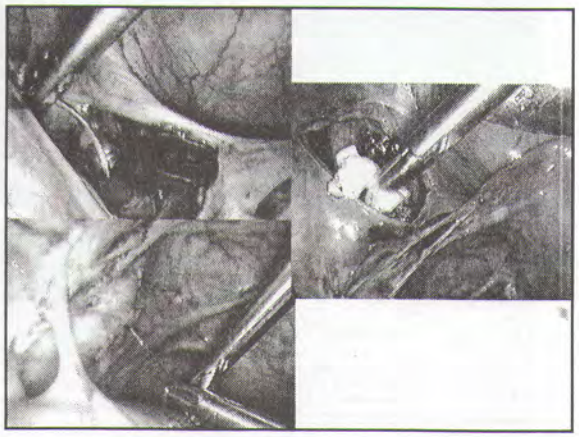












World's First Case of Ovarian Transplantation in the Forearm

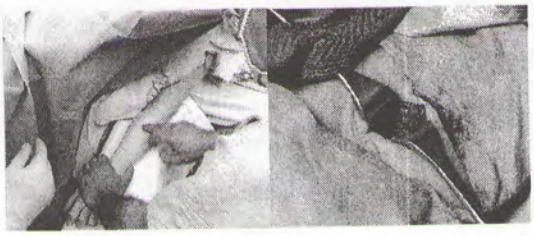
- Experience with parathyroid
- Performed under local anesthesia
- Monitored readily by:
  - palpation
  - high frequency ultrasound probes
  - antecubital vein phlebotomy for steroid output.
- Easily removed
- Egg retrieval can easily be performed

Tissue Preparation for Forearm Transplant

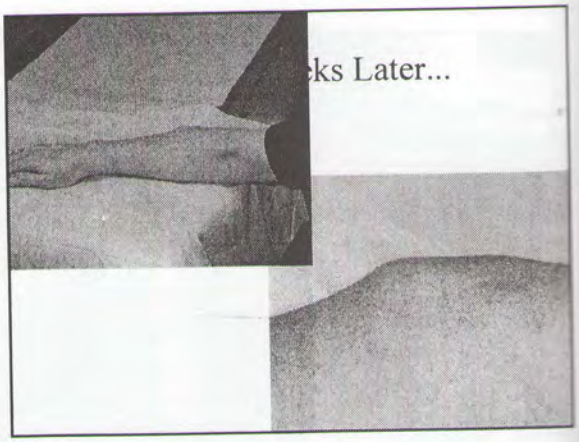
Patient Follow Up

- 9 weeks after the transplant
- The patient returns to the office with a painless "bulge" at the site of the transplant....

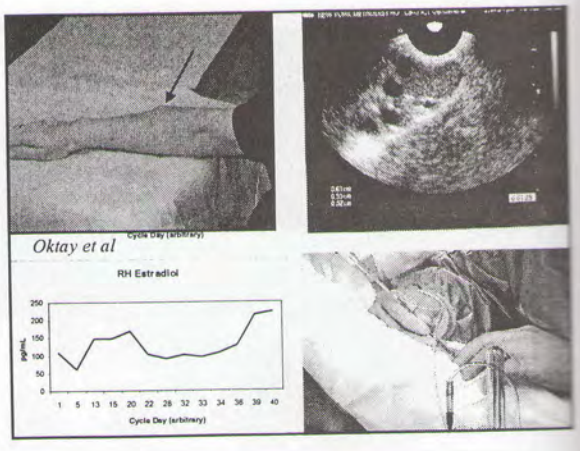
Incision



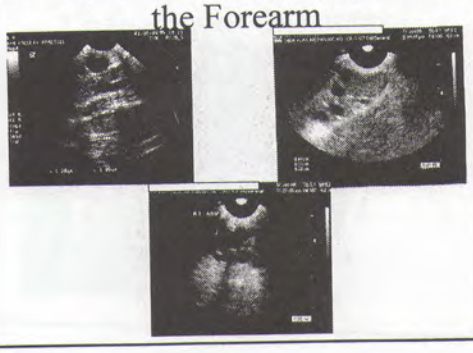
...ks Later...



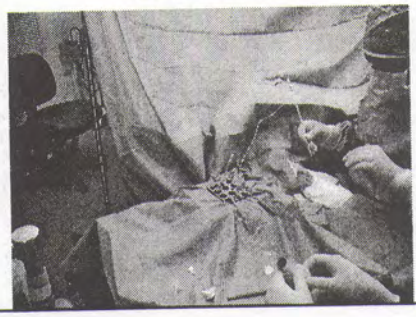
Positioning and Incision



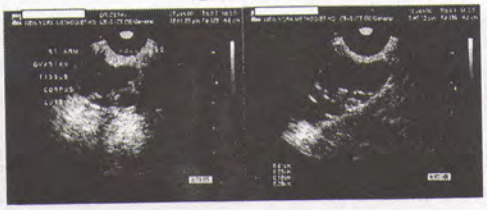
Multiple Follicle Development in the Forearm



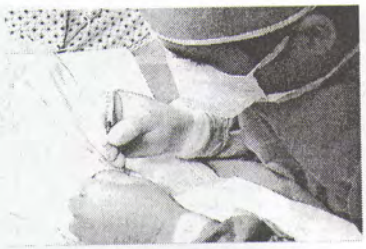
Set-Up For Percutaneous Retrieval



Multiple Follicles in the Forearm Graft

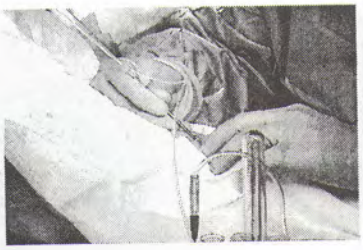


Local Anesthesia



Percutaneous Oocyte Retrieval

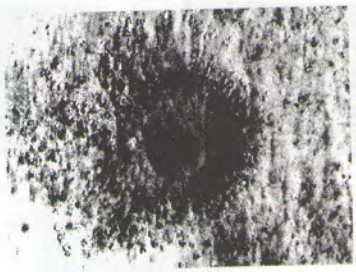
Needle Insertion



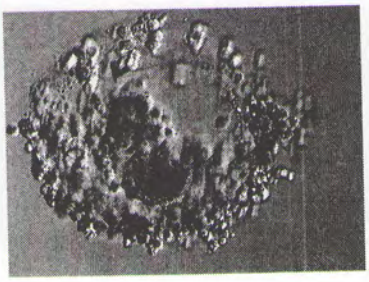
Stimulated Cycle

- Antagon down-regulation
- FSH for 7 days
- 4 follicles (largest 22x9 mm)

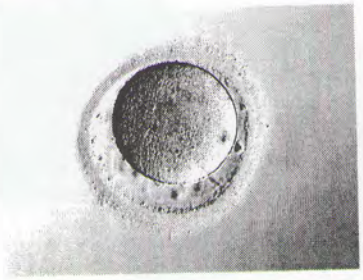
2nd egg



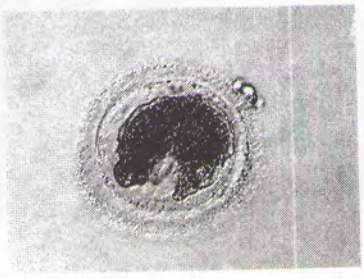
1st Egg (fractured)



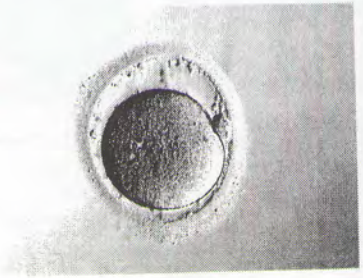
2nd egg,cleaned: M-I stage



3rd egg, atretic (cleaned)



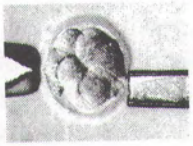
2nd, IVM'ed & ICSI'ed

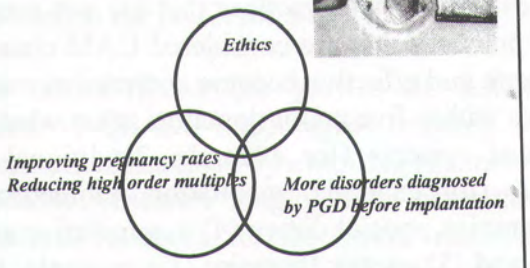


Unanswered Questions

- Guidelines for candidate selection
  - *(procedure abuse)*
- What method is most efficient?
- How much tissues are to be removed?
- Transmission of disease

Future Directions





Pak Chung, M.D. is Assistant Professor of Obstetrics & Gynecology, Center for Reproductive Medicine, Weill's Medical College of Cornell University

NCCAM Perspectives on Research on Complementary and Alternative Medicine: Past, Present, and Future

Shan S. Wong, Ph.D.

The National Center for Complementary and Alternative Medicine (NCCAM) was established in 1998 by the U. S. Congress in response to the ever-increasing use of scientifically unsubstantiated complementary and alternative medicine (CAM) therapies,[1-3] escalating expenditure of public money in the billions of dollars each year in this area,[1] and growing coverage of these therapies by third-party payers.[4] The Center is charged to conduct and support basic and applied research and research training and disseminate information with respect to identifying, investigating, and validating complementary and alternative therapies.[5] Thus, NCCAM supports a broad portfolio of grants and contracts for basic and applied research and research training to identify, investigate, and validate CAM treatments. Disseminating the results of these studies to the public and practitioners is another important priority. NCCAM prioritizes its research programs according to the relative use of a modality, the evidence supporting its value and safety, and opportunities to advance the relevant fields of science.

NCCAM Domain

CAM covers a wide spectrum of ancient to new-age approaches that purport to prevent and treat diseases. By definition, CAM practices are those healthcare practices that are not currently an integral part of conventional medicine. The list of practices that are considered CAM changes over time as CAM practices and therapies that are proven safe and effective become accepted as mainstream healthcare practices. NCCAM groups CAM practices within five major domains, acknowledging that other groupings are possible: (1) alternative medical systems (for example, Traditional Chinese Medicine, Ayurveda); (2) mind-body interventions, (for example, meditation, biofeedback); (3) biologically-based treatments (for example, herbal therapies, special diets); (4) manipulative and body-based methods (for example, chiropractic, massage); and (5) energy therapies (for example, Reiki, Qi gong). The individual systems and treatments comprising these categories are too numerous to list in this document. In addition, there is some overlap across domains such that a CAM practice included within one domain might also be classified within one or another of the five domains. For example, discrete practices such as meditation are considered mind-body interactions, but they are also included as part of some alternative systems of medicine. Readers who wish to know more about the details of these domains are encouraged to review the NCCAM Five-Year Strategic Plan.[5]

NCCAM Research Program

The appropriations to NCCAM have increased substantially from $48.9 million since 1998 when it was established to $104.5 million in fiscal year (FY) 2002. However, the amount is not sufficient to study all CAM practices.[6] Therefore, NCCAM must be selective when determining which of the many possible research opportunities it will support.[7]

NCCAM has both intramural and extramural programs. The Intramural Research Program supports the work of CAM researchers at scientific laboratories within the NIH. This program provides a foundation for NIH scientists to conduct basic and clinical research in CAM. The Extramural Research Program helps design, develop, review, fund, and implement specific CAM research projects

and training that occur outside the NIH, in addition to coordinating grants with other NIH institutes and centers.

In response to the urgent need to provide reliable information to the public, NCCAM allocates a relatively large percentage of its resources to critical clinical trials.[8] This approach is in contrast to the traditional discovery of new treatments where basic mechanisms are first investigated before a clinical trial takes place. NCCAM realizes that acquiring important basic, mechanistic, and pre-clinical information is necessary to completely understand the safety issues and to optimize research paradigms. These critical research needs are being gradually fulfilled as more resources become available and as some of the important clinical trials approach completion.

In addition to supporting focused clinical trials, NCCAM established CAM Research Centers that specialize in various disease areas such as arthritis, craniofacial disorders, neurological disorders, cardiovascular diseases, and cancer.[9] These research centers not only encourage CAM research, but also cultivate a pool of investigators interested in CAM, which is very important for the growth of the field. The topics of research involve clinical trials, pre-clinical and basic investigations involving all CAM modalities.

The majority of NCCAM supported CAM research is investigator initiated. NCCAM now supports over two hundred such projects covering all disease aspects. The modalities being studied include Tai Chi (Taiji) exercise, Hawthorn, phytoestrogens, biofeedback, Ayurvedic herbals, acupuncture, qigong, Reiki, meditation, spirituality, *Ginkgo biloba*, and special diets. A list of funded grants is posted at the NCCAM website.[10]

To further foster the growth of skilled investigators in both CAM and conventional communities, NCCAM encourages research collaborations between CAM and conventional practitioners and researchers by awarding grants to individuals as well as institutions for both mentored and independent research, ranging from basic through clinical research investigations. The program awards National Research Service Award Institutional Training Grants (T32) to eligible institutions to develop or enhance research-training opportunities for individuals, selected by the institution, who are training for careers in specified areas of biomedical and behavioral research. The NRSA also supports pre-doctoral and post-doctoral fellowships.

NCCAM Resources for Investigators

NCCAM encourages the research community to submit unsolicited applications as well as respond to solicitations. Virtually all aspects of CAM modalities are open for investigation. In addition to the traditional investigator-initiated NIH grant mechanism (R01), many other options are available. One important opportunity that researchers have is submitting an exploratory/developmental application (R21). These are relatively small, limited, two-year awards for the generation of sufficient preliminary data necessary to support a full research grant (R01). To further promote research, NCCAM also supports training and career development awards (K series). Information regarding applications and solicitations is published in the NIH Guide[11] and is available on the NCCAM website.[12]

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Commonly used Natural Products: What is safe?

David Y. Zhang MD, PhD

(The following is printed from Dr. Zhang's Power Point slides)

Change in American Health market

- **42% Americans use alternative med (198 million US population)**
- **36% in 1990 to 42% in 1997**
- **629 million visits to CAM practioners in 1997 (>> PCP)**
- **Herbal (12.1%, 10 million/per year), massage (11%), Chiro (11%), spiritual healing (7%), megavitamins (5.5%), energy healing (3.8%), homeopathy (3.4%), acupuncture (1%, 5 million/year).**
- **Back problems, allergies, fatigue, arthritis, headaches, neck problems, high BP, sprain/strain, insomnia, depression**
- **CAM Service: $21.1 billion and $12.2 billion out-of-pocket in 1997**
- **72% pt do not discuss with MDs, 89% use CAM without MD prescription**

Why do patients use CAM

Push factors	Pull factors
• Dissatisfaction with orthodox medicine – ineffective – adverse effects – poor communication with doctor – insufficient time with doctor – waiting lists	• Philosophical congruence – spiritual dimension – emphasis on holism – active role of patient – explanation intuitively acceptable – natural treatments
• Rejection of orthodox medicine – anti-science or anti-establishment attitude	• Personal control over treatment
• Desperation	• Good relationship with therapist – on equal terms – time for discussion – allows for emotional factors
• Cost of private orthodox medical care	• Accessible
	• Increased well-being

Physician's role in CAM uses

- **Protect patients against dangerous practice**
- **Permit practices that are harmless & may assist in comfort or palliation**
- **Promote & use those practices that proven safe & effective**
- **Partner with patient by communicating with them about the use of specific CAM therapies and products**

Evaluation of CAM use

- Is the CAM treatment dangerous?
- Dose the CAM therapy prevent the patient from receiving needed medical conventional treatment?
- Can the CAM therapy be continued in conjunction with conventional treatment?
- Has the pt sought out CAM therapy because of distrust or bad experience with conventional medicine?
- Is conventional medicine failing the patient in some way that may be addressed by CAM?

Useful Resources

- Jonas and Levin: Essentials of Complementary and Alternative Medicine, 1999, Lippincott
- Anderson: Clinician's guide to holistic medicine, 2001, McGraw-Hill
- Edzard Ernst: The Desktop Guide to Complementary and Alternative Medicine: an evidence-based approach, 2001, Mosby
- PDR for herbal medicine 2ed. 1999, Medical Economics
- M. Rotblatt: Evidence-based herbal medicine, 2002, Hanley & Belfus, Inc
- PDR for nutritional supplements, 2002

Variety of herbal medicine in US

- Chinese Traditional—multiple herb formula
- Greek/Roman—single herbs
- Indian
- Homeopathy
- Natraceuticals
- Naturopathy
- Western herb
- Chinese herb

Most commonly used herbs in US

- Ginseng
- Ginkgo
- Green tea
- Saw palmetto
- St John's wort
- Echinacea
- Chondroitin/glucosamine
- Ginger
- Garlic
- Kava
- Valerian

Most commonly used Chinese herbs

- Bolus of six drugs (Liuwei dihuang wan)
- Antidotal decoction of coptis (Huanglian Jiedu Tang)
- Decoction of four ingredients (Siwu Tang)
- Decoction of four noble drugs (Si Junzi Tang)
- Decoction of 10 combination (Shi Quan Da Bu Tang)
- (Qi Ju Di Huang Wan)

Active chemicals in herbal medicines

Class	Examples
Alkaloids	Colchicine, ephedrine, berberine, cocaine, caffeine
Flavonoids	Quercetin, bacailin, licoricidin, genistein
Glycosides	Digitoxin, cascarocides
Saponin	Ginsenosides, glycyrrhizin
Sterols	Ergosterol, B-sitosterol
Polyphenols	Hydroquinone, capsaicine, salicin
Terpenes	Zingiberene, ginkgolides, taxol, lycopene

Safety issues of herbal products

- Contaminants
- Herb-drug interaction
  - Pharmacokinetic
  - Pharmacodynamic
- Toxicity/adverse effects
- Adulteration
- Quality control

Contaminants found in herbs

Type of contaminant	Examples
Microorganisms	*Staphylococcus aureus*, *Escherichia coli* (certain strains), *Salmonella*, *Shigella*, *Pseudomonas aeruginosa*
Microbial toxins	Bacterial endotoxins, aflatoxins
Pesticides, herbicides	Chlorinated pesticides (e.g. DDT, DDE, HCH-isomers, HCB, aldrin, dieldrin, heptachlor), organic phosphates, carbamate insecticides and herbicides, dithiocarbamate fungicides, triazin herbicides
Fumigation agents	Ethylene oxide, methyl bromide, phosphine
Radioactivity	Cs-134, Cs-137, Ru-103, I-131, Sr-90
Heavy metals	Lead, cadmium, mercury, arsenic

Mercury and arsenic in TCM products

Preparation	Mercury	Arsenic
An Gong Niu Huang Wan	Up to 621 mg	Up to 36.6 mg
Da Huo Luo Wan	Up to 23 mg	Up to 0.1 mg
Zhusha Aushen	659 mg	?
Tsai Tsao Wan	Up to 16 mg	Up to 0.6 mg

Potential herb-drug interactions

- Affect absorption of conventional drugs
- Interfere with coagulation
- Diuretic herbs—potassium
- Hypo/hypertensive herbs
- Hypoglycemic herbs
- Immunostimulant herbs
- Phytoestrogen herbs
- Sedative herbs
- Stimulant herbs

Interaction with cardiac drugs

Name	Direction of effect	Concomitant medication
Adonis	⇧	Cardiac glycosides
Agrimony	⇧	Antihypertensives
Aloe vera	⇧	Cardiac glycosides, antiarrhythmic drugs
Arnica	⇩	Antihypertensives
Asafoetida	⇧	Antihypertensives
Avens	⇧	Antihypertensives
Bayberry	⇩	Antihypertensives
Bearberry	⇧	Cardiac glycosides
Betony	⇧	Antihypertensives
Black cohosh	⇧	Antihypertensives
Blue cohosh	⇩	Antihypertensives
Boldo	⇧	Cardiac glycosides
Broom	⇧	Beta-blockers, antihypertensives
Buchu	⇧	Cardiac glycosides
Buckthorn	⇧	Cardiac glycosides

Interaction with cardiac drugs (continued)

Calamus	⇧	Antiarrhythmics, antihypertensives,
Capsicum	⇩	Antihypertensives
Cascara	⇧	Cardiac glycosides
Cat's claw	⇧	Antihypertensives
Celery	⇧	Antihypertensives
Co-enzyme Q10	⇧	ACE inhibitors and Ca+ channel blockers
Cola	⇩	Antihypertensives
Coltsfoot	⇩	Ca+ channel blockers, antihypertensives
Cornsilk	⇧	Antihypertensives
Cowslip	⇧	Antihypertensives
Dandelion	⇧	Antihypertensives
Devil's claw	⇧	Antihypertensives
Elecampane	⇧	Antihypertensives
Ephedra	⇩	Antihypertensives
Fenugreek	⇧	Antihypertensives
Figwort	⇧	Cardiac glycosides
Fucus	⇧	Antihypertensives
Fumitory	⇧	Antihypertensives, beta-blockers, cardiac glycosides, Ca+ channel blockers
Garlic	⇧	Antihypertensives
Gentian	⇩	Antihypertensives
Ginger	⇩	Antihypertensives
Ginseng, eleutherococcus	⇧	Antihypertensives
Ginseng, panax	⇧	Antihypertensives, cardiac glycosides
Goldenseal	⇧	Antihypertensives
Hawthorn	⇧	Antihypertensives, cardiac glycosides
Horehound, white	⇧	Antihypertensives
Horseradish	⇧	Antihypertensives
Indian snakeroot	⇧	Antihypertensives
Irish moss	⇧	Antihypertensives
Kelp	⇧	Antihypertensives
Khat	⇧	Antihypertensives, antiarrhythmic drugs, beta-blockers
Khella	⇧	Antihypertensives

Interaction with cardiac drugs (continued)

Licorice	⇩	Antihypertensives
Lily-of-the-valley	⇧	Cardiac glycosides, beta-blockers, Ca+ channel blockers
Lugwort	⇧	Cardiac glycosides
Maté	⇩	Antihypertensives
Mistletoe	⇧	Antihypertensives
Motherwort	⇧	Cardiac glycosides, antihypertensives
Nettle	⇧	Antihypertensives
Night-blooming cereus	⇧	Cardiac glycosides, ACE inhibitors, antiarrhythmic drugs, Ca+ channel blockers
Oleander	⇧	Cardiac glycosides
Parsley	⇧	Antihypertensives
Pill-bearing spurge	⇧	ACE inhibitors
Plantain	⇧	Antihypertensives
Pokeroot	⇧	Antihypertensives
Prickly ash	⇧	Antihypertensives
Psyllium	⇧	Cardiac glycosides
Queen Anne's lace	⇧	Antihypertensives, cardiac glycosides
Red clover	⇧	Cardiac glycosides
Rhubarb	⇧	Cardiac glycosides
Rue	⇧	Cardiac glycosides, antihypertensives
Sage	⇧	Antihypertensives
Sarsaparilla	⇧	Cardiac glycosides
Senna	⇧	Cardiac glycosides
Shepherd's purse	⇧	Antihypertensives, beta-blockers, cardiac glycosides, Ca+ channel blockers
Squaw vine	⇧	Cardiac glycosides
Squill	⇧	Cardiac glycosides, antihypertensives, antiarrhythmic drugs, Ca+ channel blockers
St John's wort	⇧	Cardiac glycosides, antihypertensives
Strophantus	⇧	Cardiac glycosides
Vervain	⇧	Antihypertensives
Wild carrot	⇧	Antihypertensives

Interaction with anticoagulation drugs

Name	Direction
Agrimony	⇩
Alfalfa	⇧
Angelica	⇧
Aniseed	⇧
Arnica	⇩
Asafoetida	⇧
Bilberry	⇧
Black haw	⇧
Bogbean	⇧
Buchu	⇧
Cat's claw	⇧
Celery	⇧
Chamomile	⇧
Chondroitin	⇧
Cinchona	⇧
Clove	⇧
Co-enzyme Q10	⇧
Cordyceps	⇧
Danshen	⇧
Devil's claw	⇧
Dong quai	⇧
Fenugreek	⇧
Feverfew	⇧
Fucus	⇧

Interaction with anticoagulation drugs (continued)

Garlic	⇧
Ginger	⇧
Ginkgo	⇧
Ginseng, panax	⇧
Goldenseal	⇩
Horse chestnut	⇧
Horseradish	⇧
Irish moss	⇧
Kelp	⇧
Khella	⇧
Licorice	⇧
Lovage	⇧
Lugwort	⇧
Meadowsweet	⇧
Mistletoe	⇩
Mugwort	⇧
Pau d'arco	⇧
Pill-bearing spurge	⇧
Pineapple	⇧
Poplar	⇧
Prickly ash	⇧
Quassia	⇧
Red clover	⇧
Reishi	⇧
Senega	⇧
St John's wort	⇩
Sweet clover	⇧

...erative concerns of herbal medicines

Herb	Relevant phaco	Perioperative concerns	discontinuation
Echinacea	Activation of immunity	Allergy, decrease immunosuppresion	N/A
Ephedra	Inc HR, BP	Arrhythmias, MAO inhibitor	24 h
Garlic	Dec platelet agg	Bleeding	7 days
Ginkgo	Inh platelet activat	Bleeding	36 h
Ginseng	Dec glucose, dec coag	Hypoglycemia, bleeding	7 day
Kava	Sedation	Sedative effect	24 h
St John's wort	Inh MAO, neurotransmitter,	Inh P450, dec digoxin	5 day
Valerian	Sedation	Sedative effect,	N/A

...eraction with antibiotics

Name	Direction
Alfalfa	⇧
Aloe vera	⇧
Basil	⇧
Bee pollen	⇩
Burdock	⇧
Celandine	⇧
Celery	⇧
Coriander	⇧
Cornsilk	⇧
Damiana	⇧
Dandelion	⇧
Devil's claw	⇩
Elecampane	⇩
Eucalyptus	⇧
Fenugreek	⇧
Figwort	⇩
Garlic	⇧
Ginseng, eleutherococcus	⇧
Ginseng, panax	⇧
Gotu kola	⇩
Guar gum	⇧
Horehound	⇧
Hydrocotyle	⇩
Juniper	⇧
Licorice	⇩
Marshmallow	⇧
Melatonin	⇧
Myrrh	⇧
Myrtle	⇧
Nettle	⇧
Night-blooming cereus	⇧
Onion	⇧
Sage	⇧
St John's wort	⇩
Tansy	⇧

Interaction with OCP

Name	Direction
Chaste tree	⇧
Guar gum	⇩
Herbal laxatives (e.g. aloe vera, senna)	⇩
Hop	⇧
Licorice	⇩
Pokeweed	⇧
Red clover	⇧
Siberian ginseng	⇧
St John's wort	⇩

Recommend therapeutic monitoring

Aloe	Renal function, electrolytes
Angelica	Coagulation studies
Basil	Blood glucose
Bayberry	Liver function tests
Bearberry	Renal function, electrolytes
Bee pollen	Blood glucose
Betony	Liver function tests
Bistort	Liver function tests
Black haw	Coagulation studies
Blackroot	Liver function tests
Blue cohosh	Blood glucose
Boneset	Liver function tests
Borage	Liver function tests
Buchu	Liver function tests
Cascara	Renal function, electrolytes
Castor bean	Renal function, electrolytes
Cat's claw	Coagulation studies
Chaparral	Liver function tests
Chondroitin	Full blood count, coagulation studies
Condurango	Liver function tests
Cowslip	Liver function tests
Cucumber	Renal function, electrolytes
Dandelion	Blood glucose
Dock, yellow	Renal function, electrolytes
Dong quai	Coagulation studies
Fenugreek	Coagulation studies, blood glucose
Garlic	Full blood count
Ginger	Coagulation studies
Gingko	Coagulation studies
Ginseng	Blood glucose
Gotu kola	Blood glucose
Horse chestnut	Coagulation studies
Jaborandi tree	Liver function tests
Kava	Full blood count
Kelp	Coagulation studies
Kelpware	Renal function, electrolytes, coagulation studies, blood glucose
Khella	Liver function tests
Lovage	Renal function, electrolytes
Lungwort	Coagulation studies
Marshmallow	Blood glucose
Mayapple	Full blood count, liver function tests, renal function, electrolytes
Myrrh	Blood glucose
Myrtle	Blood glucose
Pau d'arco	Coagulation studies
Pennyroyal oil	Liver function tests, renal function, electrolytes
Pomegranate	Liver function tests
Poplar	Liver function tests, coagulation studies
Ragwort	Liver function tests
Red clover	Coagulation studies
Rhatany	Liver function tests
Royal jelly	Blood glucose
Sage	Blood glucose
Sarsaparilla	Renal function, electrolytes
Shark cartilage	Liver function tests
Skullcap	Liver function tests
Soapwort	Liver function tests, renal function, electrolytes
Sorrel	Liver function tests, renal function, electrolytes
Squaw vine	Liver function tests
Tonka bean	Liver function tests, coagulation studies
Turmeric	Coagulation studies
Valerian	Liver function tests
Willow	Liver function tests, renal function,

Toxicity of commonly used herbs

Herbs	Adverse effects
Ginseng	Hypertension, HA, dizziness, nasal/vaginal bleeding; ginseng abuse syndrome-HTN, insomnia, depression, amenorrhea, edema
Arnica spp	Gastroenteritis (tea)
Saw palmetto	Gastric complains
St John's wort	Allergic reaction, fatigue, photosensitivity
Coptis spp	Jaundice (G-6PD deficiency)
Taxus celebica	Fever, GI upset, acute renal failure (large dose)
Tripterygium wilfordii	Skin rashes, amenorrhea, leukopenia, liver toxicity, oligospermia.

Adverse effect reported in CAM-related RCTs

- Total 27 out of 121 RCTs with AE
  - Herbs 22
  - Vitamins 2
  - TCM 2
  - Pulsed electromagnetic fields 1
- Mean Duration 10.3 wks, mean sample size n=89
- Adverse effects: 17 of 565 subjects (3%)
- Compare to conventional (9 RCTs)
  - 6 of 9 CAM has a lower AE rate over conventional
  - 1 of 9 CAM has a increased AE rate
  - 2 of 9 has no difference

Adulteration

Product	Adulterant
PC-SPEC	Warfarin
SPES	Alprazolam
Gan Mao Tong Pian	Diclofenac, phenylbutazone
Chuifong Toukuwan	Diazepam, Diclofenac, Dexamethasone
Fang chi	Stephania tetrandra→Aristolochia fangchi
Mu Tong	Akebiae Caulis→Clemais armandi or Aristolochia manshurensis

PC-SPES, SPES (BotanicLab)

- **PC SPES--prostate health**
  - **Warfarin/Coumadin**
- **SPES -- strengthening the immune system.**
  - **Alprazolam/Xanax**
- **BotanicLab, the manufacturer of the products, has voluntarily recalled PC SPES and SPES nationwide.**
- **California Department of Health Services (3/2002)**

***Aristolochia fangchi*-induced nephorpathy and carcinoma**

- **Chinese-herb nephropathy-- weight-reducing pills containing Chinese herbs**
- ***Stephania tetrandra* → *Aristolochia fangchi* (manufacturing error)**
- **Terminated in Belgium in 1992**
- **39 patients of 105 patients with Chinese-herb (*A. fangchi*) nephropathy--prophylactic surgery**
- **18 cases of urothelial carcinoma , 19 mild-to-moderate urothelial dysplasia, 2 normal urothelium.**
- **Aristolochic acid–related DNA adducts in tissues**
- **Cumulative dose of aristolochia > 200 g with a higher risk of urothelial carcinoma.**

QC issues

- **No government regulation**
  - **United States Pharmacopeia (USP)**
- **Factors affect quality**
  - **Growing condition and location**
  - **Method of drying and grinding**
  - **Method of processing**
  - **Storage**
- **Standardization**
  - **Active ingredient**
  - **Variation of the ingredients**
    - **5-40 fold different**
    - **No ingredient**

Regulation

- **FDA**
  - **Dietary Supplement Health and Education Act (DSHEA, 1994)**
    - **Herbal products:**
      - **Food--Soybean label**
      - **Food supplement**
  - **Botanical drug products guidance (8/2000)**
    - **Drug: Topical, OCT, Rx**
    - **Safety, Toxicity**
    - **GAP, GLP, GMP**

How to recommend herbal products

♦Products used in RTC
-Ginkgo GBE
-Ginsana
♦www.ConsumerLab.com
-St. John's wort, ginsengs, ginkgo, saw palmetto, glucosamin, etc
♦USP standards with NF label
♦Pharmaceutical firms
-Boehringer-Pharmaton
-American Home Products

♦Cheap ≠ effective

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The Brown Bag Problem and Traditional Chinese Medicines

Elaine Kang-Yum, Rph., CSPI

Background

The practice of Tradition Chinese Medicine (TCM) has been a treasured element of the Chinese cultural heritage as we know it and respect it. Chinese herbal medicines (CHM), a component of TCM, in particular has gained an augmented global popularity and vigilance in recent decades. With the influx of Chinese immigrants to the United States on the rise, the utilization of CHM has permeated the Chinese-American health care system [1]. In addition, CHM has come into vogue with the non-Asian health conscious generation, posing more challenges to the already stressed health care system. Despite the availability of advance modern therapeutic modalities, a confluent of factors have contributed to CHM consumers remaining ardent in their choices. Although the popularity of CHM is undulating, it has not received the same vigilance as allopathic medicines due to its non-drug status in the U.S.[2]

When used properly, traditional CHM has been perceived as safe and is well accepted as an effective therapeutic modality by its users. However the misuse, abuse, improper preparation and adulteration of certain CPM may lead to co-morbidity and toxic situations. As more people turn to alternative medicines, the brown bag problem will inexorably engender a tremendous challenge for consumers and practitioners alike. Since patients who utilize herbal products may not always be candid with their allopathic practitioners about their complementary regimen, potential herb-related adverse effects and interactions may be overlooked and remained unreported. Despite the wide array of products on the market, having a general knowledge of some common herbal ingredients and their properties will be helpful in avoiding certain adverse incidences.

Although advances in computer informatics have raised the level of cognizance and prudence in the utilization of CHM among the general population, studies have shown a lag between awareness and communication among the medical communities. The lack of published data and resources is considered as a major area of deficiency.[3] In a health care system where Eastern and Western medicines co-exists, the public health agenda must encompass raising the level of awareness and knowledge of complementary practices. Allopathic practitioners must have the confidence to suspect adverse reactions and diagnose toxicities related to the use of CHM and promptly report them to the FDA. Effective communication on all levels is imperative in ensuring safety and preventing co-morbidity in patient care.[4]

Objectives

- Define the practice of CHM.
- Discuss problems associated with foreign and domestic CHM.
- Discuss various CHM related adverse reactions.
- Discuss various herb-drug interactions and co-morbidities.
- Discuss recent recalls and warnings.
- Provide useful websites resources.

I. The practice of Chinese herbal medicine

- **Chinese Herbal Medicines (CHM)** 中草藥 – A component of TCM that utilizes medicinal botanicals for healing and promotion of health based on accumulated empirical experiences.
- **Chinese Herbal Formulas (CHF)-**中藥方劑- CHM prescriptions comprise of herbs, plants, minerals and dried animal parts which requires meticulous preparation into decoctions or teas before consumption.
- **Chinese Patent/ Proprietary Medicines (CPM)--** 中國成藥
  Processed CHF that are formulated into pill or liquid form for ease of use. CPM products are readily accessible on the shelves of Chinese stores without a prescription.[5]

CHM products are considered dietary supplements in the U.S.; hence the FDA does not regulate it as drug substances. Under the FDA **Dietary Supplement Health and Education Act of 1994 (DSHEA),** manufacturers and consumers can enjoy the profits of these products with few restrictions. Although the offices of the FDA have been given the authority to establish Good Manufacturing Practices (GMPs) regulations and guidelines that restricted product advertisements to claim cures for illnesses, the policing by the administration is a daunting task.[6]

II. Problems with CHM

A. Product QA Factor

- Inter-product variability – same brand of product manufactured and distributed by different companies presents differences in quantity and quality of ingredients.
- Intra-product variability – same brand of products lacking uniformity in quality and quantity of ingredients from lot-to-lot.
- Errors in substitution of herbs- replacing original ingredients with more toxic ones.
- Adulteration with western medicines – intentional incorporation of western drug entities to enhance the effects of the product.
- Heavy metals were detected as intended ingredients or as adulterants in products causing health consequences.
- Product labeling– some labels do not reflect the actual ingredient. Product information differences in Chinese and English, often making health claims in the Chinese only.
- Products lack expiration date and handling instructions.[2,7,12]

B. Adverse Reactions and toxicity

- ADR to naturally occurring medicinal in the compounds (i.e. ginseng, licorice)
- ADR to natural toxins in the compound (i.e. cinnabar, aconite)
- ADR to contaminants in the compounds (i.e. western drug entities, heavy metals)
- ADR due to over dosage (i.e. ma huang , ch'an su)
- ADR due to herb-drug interactions (i.e. dang gui and warfarin)
- ADR due to complication from pre-existing diseases (i.e. hepatic, renal)

III. Diagnosis and Evaluation of Co-Morbidities

A. Herb-drug interactions can be a potential problem when patient presents with a multi-regimen profile. It is especially important if patients are concomitantly using other pharmaceutical products with narrow therapeutic indexes. Practitioners must exercise prudence in screening patient's medical history and encourage discussion of concerns.

Table 1. Selected herb-drug interactions [5,9,10,11,16,19.18,20]

Herb 中藥	Drug 西藥	Signs & Symptoms	Mechanism
Dan-shen 丹參	Warfarin	Inc.INR; gastric bleeding	Possibly additive action due to coumadin.
Dong quai 當歸	Warfarin	Inc. INR, bruising	Herb acts as Cox inhibitor
Ginko biloba 銀杏	Trazadone	Coma	Herb has antiplatelet activity.
	Warfarin	Parietal hemorrhage	May decrease effect of warfarin.
	Aspirin	Hyphema	
Panax Ginseng 人參	Warfarin	Dec. INR	Herb has antiplatelet activity.
	Phenelzine(MAOI)	Manic s/s, insomnia, headache, tremor, visual hallucinations. Hyperglycemia	May decrease effect of warfarin.
Licorice 甘草	Hydrocortisone	Vaginal bleeding	Estrogenic effects
		Pseudoaldosteronism Hypertension	Potentiates the cutaneous vasoconstrictor response.
		Accute flaccid tetraparesis Hypokalemia	Na retention
	MAOI		
	Spironoacltone	Hypertension	
	Estrogen products		Estrogen sites binding.
	Warfarin	^INR, ^bleeding	
Ginger 干姜	Warfarin	^INR, ^bleeding	Potent thromboxane synthetase inhibitor
Chan su 蟾酥	Digoxin	Digoxin like reaction. Dig. toxicity	
Black Cohosh 升麻	Estrogen products		Estrogen sites binding
	Warfarin		Forms tannin complex that inhibits Fe absorption.
	Iron		
Dahuang 大黃	Antibiotic	Dec. effect	Alters absorption
	Vit. B1 & B6	Dec. effect of both	Irriversible binding
	Salicylates		
	Caffeine		
Fenugreek 胡蘆巴	Warfarin	^bleeding	
	Estrogen products	^ uterine contraction	
Methyl Salicylate 柳酸甲酯	Salicylates	Salicylism	Over dose

B. Herb-disease co-morbidity is an important consideration when certain herbs are used in patients with existing disease and conditions. Disease states that may alter the immune response, metabolism and excretion of herbs are particularly of concern. The lack of safety statistics warrants contraindications in pregnancy and breastfeeding. Factors that may influence the diagnosis of herb related morbidity includes method of preparation, dose ingested and duration of exposure to the herbal product.

Table 2. Selected herb-disease co-morbidities[16,20,25]

Disease/ Condition	Herb	Effect
Neurological	Datura metel L.	Neurpathy
	Borneol	Lowers seizure threshold
Gastrointestinal	Realgar, Cinnabar and other gastric irritants.	Various GI disorders
Cardiac	Licorice	Hypertension
	Bufo secreta	Dig-like effects
Hepatic	Artemisia scoparia, coptis chinensus, huanglain	hyperbilirubinemia
Renal	aristolochic acid	Interstitial renal fibrosis
		Proteinuria
Hematologic	gingko, dang gui, ginger,	Increase bleeding
	ginseng, licorice	Effects glucose tolerance

C. Products Warnings and Recalls.

Since herbal medicinal are not regulated as drugs in the U.S., it is not required to be intensively tested for safety and efficacy before marketing. The FDA monitors public safety through the **MedWatch** system, and is reliant on information provided to the administration by various sources. Public safety warnings and recalls are issued when a reported adverse event related to a product has been investigated. The poison control center network plays an important role in managing cases and data collection. Although not mandated, the collaborative efforts of the general public and health care community in the reporting of herbal product related adverse effects are necessary in providing more studies and resources.

MedWatch

Website : http://www.fda.gov/medwatch
Telephone : 1-800-FDA-1088
Fax: 1-800-FDA-0178Medwatch FDA Office of Emergency : 301-443-1240

IV. Patient Communication

A. Mis-communication Factors

- Language barriers between patients and practitioners.
- Patients are apprehensive about revealing their CHM usage fearing disapproval.
- Patients view CHM, as natural products therefore do not need prudence.
- Allopathic practitioners avoid discussions with patients due to lack of knowledge.
- Foreign patients seeking temporary health care without known medical history.
- Under reporting of ADR and co-morbidities due to lack of education & resources.

B. Practical guidelines for patients using herbs

- Purchase herbs only from reputable suppliers.
- Do not take large quantity of any one herbal preparation.
- Do not use herbs if you are pregnant or nursing.
- Do not give herbs to young children without professional advice.
- Discontinue use if suspecting adverse effect.
- Communicate your supplementary product usage to your physician. [26]

Conclusion

As people become more health conscious, there is a propensity for personal autonomy in health care decisions. The choice of treatments often reflects variables that are congruent to an individual's own values and beliefs regarding health and illness. Given a modernized and well-controlled milieu, Traditional Chinese Medicine would be invaluable in the fight against diseases. However, in a multi-cultural health care system where Eastern and Western medicine co-exists, inadequate training of practitioners and lack of resources can lead to potential problems. Since CHM is considered dietary supplements, the FDA have limited authority to regulate its market in the U.S. Hence consumers are placed in a "take at your own risk" situation where "safety" is addressed only after products has been proven "unsafe".[6, 8] The sale and use of CHM will continue to grow in light of soaring health care costs. The medical community must be cognizant of the growing trends of alternative practices and be prudent in screening and documenting their patient population for possible herb related co-morbidities. A particular attention must be directed towards health care needs of the growing population of Chinese-American in our communities. Language and cultural barriers must not be a hindrance in proper care of this group of population who are prevalent users of CHM.

Helpful Websites

- http://www.LISTSERV@VM.CFSAN.FDA.GOV
- http://www.cfsan.fda.gov/~dms/
- http://www. NaturalhealthWeb.com
- http://www.Cathayherbal.com
- http://www.Cintcm.ac.cn/edata/index
- http://www.Icm.cuhk.edu.hk/icm
- http://www.Ncbi.nlm.nih.gov/PubMed
- http://www.familydoctor.com.cn
- http://www.medonline.com.cn/
- http://www.cmj.com
- http://www.nutrition.org
- http://safetyalerts.com

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22 California Dept of HS, State Health Director Warns Consumers About Prescription Drugs in Herbal Products. Feb 15, 2002

23 U.S. FDA, Sino American Health Products, Inc., Issues National Recall. Feb 18, 2000

24 U.S. FDA, dietary Supplement Firm Signs Consent Decree with FDA to Stop Selling Products Containing Ephedrine Hydrochloride. April 15, 2002

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Is Acupuncture Effective for the Treatment of Chronic Pain? An Objective Assessment

Bryan O'Young, M.D.

Rising Interests in Complementary Medicine (CM)

- Increased use of CM from 34% in 1990 to 42% in 1996
- Visits to CM practitioners increased from 400 million in 1990 to 600 million visits in 1996 per year
- Amount spent on CM visits rose from $14 billion in 1990 to $27 billion in 1996 -- most of it not reimbursed
- Over 75 medical schools offer courses on CM
- More hospitals are developing complementary and integrated medicine programs
- Health insurers are providing expanded benefit packages including CM
- Biomedical research organizations are investing more funds into the investigation of CM practices
- AMA recently devoted an entire issue on each of their journals to CM

Why the Rising Interests?

- Dissatisfaction with orthodox medicine in treating chronic disease
- Emphasis on self-healing
- Emphasis on healthy lifestyles
- Address spirituality
- Adverse effects of conventional therapies
- Escalating costs of conventional health-care

CM Is Here to Stay

The Need for Scientific Evidence

- Applying scientific methods to medicine is a relatively recent phenomenon
- The randomized controlled trial has been developed within the past 50 years
- Statistical principles and approaches for analyzing large data sets have also recently evolved

Frequently Used Methods of Investigation in Medical Research

- Qualitative research: Includes detailed case studies and patient interviews
- Laboratory and basic science approaches
- Observational studies: Includes outcomes research and other forms of observational research
- Randomized controlled trials
- Meta-analysis, systematic reviews and expert review and evaluation
- Health services research: examines the actual use and impact of interventions in context of social factors including costs and patient compliance

Acupuncture

History

- Greater than 2500 years old
- Did not gain popularity in the U.S. until 1971 when James Restin reported in the NY times how his postoperative pain after an appendectomy was relieved by acupuncture
- 1996 FDA classified acupuncture as a medical device
- 1997 NIH Consensus Conference showed "clear evidence" of acupuncture efficacy in various clinical conditions and was deemed appropriate as part of comprehensive care for others

Scientific Studies to Show the Analgesic Effects of Acupuncture

- Two types of analgesia identified
- Endorphin dependent analgesia
- Monoamine dependent analgesia

How Does Acupuncture Reduce Pain?

- Many studies performed
- Complex mechanism of neurohumeral effects to cause analgesia at a distance

What is the Latest Clinical Research Evidence for the Effectiveness of Acupuncture and Chronic Pain ?

Is Acupuncture Effective for the Treatment of Chronic Pain? A Systematic Review
(Jeanette Ezzo, Brian Berman, et at. 2000 International Association for the Study of Pain)

- Objective: Assess the effectiveness of acupuncture as a treatment for chronic pain within the context of methodological quality of the studies
- Literature Search: Medline(1966-99), 2 complementary medicine databases, 69 conference proceedings, bibliographies of other articles and reviews
- Inclusion criteria: randomized, comparison group, pain longer than 3 months, needles rather than surface electrodes, in English
- Data extracted by 2 independent reviewers using a validated instrument

- 51 studies met inclusion criteria representing 2423 chronic pain patients
- Quality of each research study was assessed by the following factors:
  A. Randomized? Score 0/1
  B. Randomization scheme described and appropriate? Score 0/1
  C. Double blind? Score 0/1
  D. Double blinding method appropriate? Score 0/1
  E. Description of dropouts and withdrawals? Score 0/1
- Scoring for the above scale A+B+C+D+E = 5 possible points **0-2 low quality, 3-5 high quality**

- Outcomes: Positive, Neutral or Negative
- P value of <0.05 defines significant outcome
- Outcome assessment using the best evidence synthesis method (Slavin 1995)
  1. Strong evidence: Multiple, relevant high quality RCTs with generally consistent outcomes (GCO)
  2. Moderate evidence: One relevant high quality RCT and one or more relevant , low quality RCTs with GCO
  3. Limited evidence: One relevant , high quality RCT or multiple relevant, low quality RCTs with GCO
  4. Inconclusive evidence: Only one relevant , low quality RCT, no relevant RCTs or RCTs with inconsistent outcomes

- Results
- 2/3 of trials received a low quality rating
- Acupuncture compared to:
- No treatment : All had positive outcomes but were low quality. Limited evidence that acupuncture is more effective than no treatment. (Level 3)
- Physiologically inert control: Inconclusive evidence
- (Level 4)
- Sham acupuncture: Inconclusive evidence (Level 4)
- Standard Care: Inconclusive evidence (Level 4)
- Most of the high quality studies with positive findings pertain to musculoskeletal (MSK) pain
- Effectiveness of acupuncture for MSK pain appears promising

Conclusion

- Limited evidence that acupuncture is better than no treatment (waiting list)
- Premature at this time to draw conclusions about how effective acupuncture is compared to placebo, sham acupuncture, or standard care for the treatment of chronic pain

Limitations

- Only English literature
- Data not stratified in terms of patient's preference and expectations toward acupuncture

Suggestions for Future Research

- Positive outcomes associated with lower methodological quality
- Therefore, more high quality trials are needed to answer the effectiveness of acupuncture
- High quality studies cluster in the sham acupuncture control group with high sample size requirements, larger trials needed
- Standardized acupuncture procedure

Teasing Apart Quality and Validity in Systematic Reviews: (An Example From Acupuncture Trials in Chronic Neck and Back Pain Smith, Lesley; Et Al. Pain 2000 May; 86:119-132)

- Extensive Literature Search
- 13 randomized controlled trials
- 281 received acupuncture and 256 received placebo
- Control (Placebo) group includes those received sham acupuncture, sham TENS, no treatment, or on waiting list
- Oxford Pain Validity Score to determine quality of study.

- Results
- Generally low quality trials with a number of methodological flaws
- Trials with low validity scores were more likely to show a benefit of acupuncture whereas trials with positive scores were more likely to show no benefit of acupuncture over placebo
- No convincing evidence that acupuncture is more effective for the relief of back or neck pain

Acupuncture and Chronic Pain Management (Lee TL. Ann Acad Med Singapore 2000 Jan;29(1):17-21)

- Review is based on the result of previous reviews, meta-analyses, and consensus conference Search: MEDLINE (from 1966), EMBASE (from (1980) and Cochrane library (1999, Volume 1)
- Only randomized trials included
  Most of the studies were of poor methodological quality
  Need for further high quality randomized controlled trials

Randomized Trial of Acupuncture Compared with Conventional Massage and Sham Laser Acupuncture for Treatment of Chronic Neck Pain (Irnich, Dominik, et al British Medical Journal Volume 322 June 30, 2001)

- Prospective randomized , placebo controlled trial
- 177 participants with chronic neck pain
- Results: One week after five treatments the acupuncture group showed a significantly greater improvement in motion related pain compared with massage but not compared with sham laser.
- Conclusion: Acupuncture is an effective short-term treatment for patients with chronic neck pain, but there is only limited evidence for long-term effects after 5 treatments.

Acupuncture and chronic pain: (A criteria-based meta-analysis: ter Riet G, Kleijnen J, Knipschild P J Clin Epidemiol 1990;43(11):1191-1199)

- 51 controlled clinical studies
- Quality of even the better studies proved to be mediocre
- Efficacy of acupuncture in the treatment of chronic pain remains doubtful

Limitations in General

- Selecting appropriate controls
- Double blind research study
- Variability of acupuncture techniques

- Difficulty of standardizing acupuncture treatments
- Inadequate population size
- Significant variability in the response to treatments
- Use of a distinctive terminology
- Importance of practitioner's experience
- Use of short term and long term follow-up

Complementary Medicine

- Medline search
- Very few controlled trials
- No conclusive evidence that complementary medicine is better than standard treatment at this point

Points to Consider

- To refer, might be more valuable to know which patients are seen in the CM practice
- How they are treated
- Whether they are satisfied
- Their outcomes
- Rather than relying on the results of small scale, placebo-controlled randomized studies done in another continent with practitioners and populations quite different from those in the patient's community

Finding the Science in Art is the Art of Science

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Stroke among Chinese American in New York City

Sun-Hoo Foo, M.D., FRCP(C), FACP, FAAN

Introduction

Stroke is a devastating disease, a leading cause of death and disability worldwide. Risk factors profiles and stroke types effect the treatment strategy for this preventable disease. The epidemiology of stroke has been widely studied among white and black patients. However, little is known about the characteristics of stroke among Chinese Americans although they are one of the fastest growing ethnic groups in New York City. This presentation is a summary of several clinical studies of stroke patients admitted to New York Downtown Hospital since 1985. Hopefully through these efforts, there will be increase awareness and effective prevention/ treatment strategies for this serious illness in the Chinese American communities can be implemented.

NYU Downtown Hospital is a community hospital at lower Manhattan. In the year 2000, there were 12,291 patients' discharge, of which 48.2% come from Manhattan, 24.9% from Brooklyn, 17.0% from Queens. Of the patients from Manhattan, 83% came from five zip codes: the top three of this were 51.8% from Chinatown (zip 10002), 16% from Downtown (zip 10038), 16% from Tribeca/Chinatown (zip 10013). Stroke is the 5th most frequent diagnosis at NYUDT Hospital. In the same year, there were 263 stroke admissions: 60.1% of the stroke patients were Chinese, 16% White, 10% African-American.

Under the leadership of Dr. George Liu, Chinese Physician Partnership was formed in 1995 and this subsequently led to the formation of the *Chinese American IPA (CAIPA)* in 1997. As of today, there are 222 CAIPA Chinese American physician service the NYC Chinese community, of which Oxford/CAIPA covers 27,919 residents (7,803 Medicare). 57% of the CAIPA members are primary care physicians, many of them use NYU Downtown Hospital for hospital admission. It therefore provides a large part of the hospital care for Chinese Americans covered by CAIPA in the three major NYC Chinese communities, especially Manhattan (In year 2000, 25.8% of zip code 10002's total 11917 admission were to NYU Downtown Hospital). Chinese stroke patients in NYU Downtown Hospital represent a cross section of the three local Chinese communities, Manhattan Chinatown in particular.

According to health care association of NY State, June 19, 1998, *stroke risk index* of the young people (less than 65 years old) in and around Chinatown is *1.45 times higher* than other communities. From 1998 to 2003, lower Manhattan population is expected to grow by 5%, but Asian population is expected to grow by 11%, elderly Asian population (>65) is expected to increase by 17%. It is not hard to imagine the impact of future strokes to this community and society at large if the trend is not reversed.

Chinese stroke in NYU Downtown Hospital Vs Northern Manhattan Stroke Study

We first did a retrospective analysis of Chinese stroke patients between year 1994-5 (N=108) and compared their social demographics and vascular risk factors which White patients in Northern Manhattan Stroke Study. *Chinese stroke patient is younger* (73 vs. 80, P<. 001) They were *more untreated hypertension* (23% vs. 6%, P<. 001), more left ventricular hypertrophy (33% vs. 9% P<. 01),

higher initial diastolic pressure (32% vs. 17% P<. 05). Although fewer Chinese patients smoke (11% vs. 17%), those who do smoke, smoke more packs per day (1.3 packs vs. 0.17 pack P<. 001)[1]

We then reviewed additional stroke patients in NYUDH from January 1995 to July 1998. Findings of the Chinese patients between these two periods of studies were analyzed. The average ages of the Chinese patients for these two studies were 71.5 years (1994-5) and 73 years (1995-8) respectively. The frequencies of stroke risk factors were similar in these two periods of studies: untreated hypertension (23% and 23%), left ventricular hypertrophy (37% and 33%), diabetes mellitus (33% and 38%), current smoker (12% and 11%), alcohol (8% and 7%), except hypertension (76% and 68%*), and cardiac disease (28% and 19%*)* P<0.05.

Stroke Patients in NYU Downtown Hospital

Of the 843 stroke patients admitted during 1995-98, there were 499 Chinese, 153 Whites, 88 blacks, 99 Hispanics and 4 other Asian. Compared to other race/ethnic groups, Chinese and white stroke patients were older, 71.5 (Chinese), 69.7 (whites) vs. 62.6 (blacks), and 64.9 (Hispanics) (p<0.01). Chinese patients had lower body mass index (22.8 vs. 26.1, 26.2 and 25.2 respectively) (p<0.01), less likely to smoke (11.8% vs. 22.2%, 22.7 and 32.3%, p<0.01), less likely to drink alcohol regularly (7.8% vs. 28.1%, 34.1% and 29.3%, p<0.01). Chinese and blacks were more likely to have history of hypertension (75.6%, 62.7%, 77.3%, 65.7%, p<0.01); Whites had the lowest incidence of left ventricular hypertrophy (37.5%, 24.8%, 37.5%, 38.4%, p<0.01). Chinese patients were more likely to have higher blood cholesterol (204,192,192,197, p<0.05) and Diabetes (33%, 21%, 24%, 28%, p<0.05), higher admission blood glucose like blacks (161 mg/dl, 145,161,153 p<0.01), Compared with other race/ethnic groups, Chinese had the *highest risk of hemorrhagic stroke* (19.2% vs 12.4%, 12.5% and 11.1% p<0.05). It is higher than any previous published US cerebral hemorrhage incidence which is usually between 8 -12.9%.

Overall hospital mortality was 12% with no significant difference between groups. Hemorrhagic stroke was more likely to be fatal than ischemic stroke (35.3% vs. 7.0%, p<0.001). [2] [3](table1).

Cerebral Hemorrhage vs. Cerebral Infarction among Chinese

Among the Chinese patients, those with *hemorrhagic stroke tends to be younger* (68.4 vs. 72.4), have higher systolic and diastolic pressure on admission and higher incidence of left ventricular hypertrophy (47.3 vs. 35.8%). Higher WBC (11.6 K vs. 9.2 K), higher complications (62.7 vs. 28.2%) and in hospital death rate (34.5 vs. 6.1%). The odd ratio of *hospital deaths* among hemorrhagic stroke patients is *5.43 vs. 1* of ischemic stroke. The ischemic stroke patients on the other hand tends to have higher triglyceride level, higher incidence of diabetes (36.9 vs. 20.9%), higher platelet count (226 vs. 204K). All the above is statistically significant.

Controlling for age and gender, the variables significantly predictive of hospital deaths for Chinese stroke patients (odds ratios and 95% confidence interval) are hemorrhagic stroke (5.53, 1.96-15.61), history of diabetes mellitus (2.64,1.35-5.20), history of heart diseases (2.01,1.02-4.19), elevated blood sugar (1.67,1.50-1.84), elevated systolic hypertension (1.58,1.36-1.78), WBC (1.26,1.06-1.50).[4] [5](tables 2,3).

TABLE 1. DIFFERENCES IN CLINICAL CHARACTERISTICS BETWEEN CHINESE AND WHITE STROKE PATIENTS

	Chinese	Whites	p-value
Patient number	454	115	
Age (years)	71.4	71.7	0.97
Male (%)	51	54	0.24
BMI (Kg/M^2)	22.8	**25.8**	**0.02**
SBP (mmHg)	155	155	0.98
DBP (mmHg)	87	86	0.86
Hypertension (%)	**77**	64	**0.03**
LVH on EKG (%)	**37**	25	**0.02**
History of IHD (%)	28	**46**	**<0.01**
Atrial fibrillation on EKG (%)	17	20	0.59
Cholesterol (mg/dl)	**204**	192	**0.01**
Triglyceride	**131**	126	**0.05**
Glucose (mg/dl)	**161**	145	**<0.01**
History of Diabetes (%)	**33**	21	**0.01**
Drink alcohol (%)	8	**25**	**<0.01**
Current smoker(%)	13	**20**	**<0.01**
Hemorrhagic stroke (%)	**24**	**17**	**0.02**
Age adjusted death rate (%)	13.8	14.8	**0.1**

TABLE 2. DIFFERENCES OF CLINICAL CHARACTERISTICS OF HEMORRHAGIC AND ISCHEMIC STROKE AMONG CHINESE PATIENTS

	Hemorrhagic	Ischemic	P-value
Patient number	110	334	
Age (years)	**68.4**	72.4	**0.006**
Male (%)	56	49	0.28
BMI (Kg/M^2)	22.8	22.8	0.953
SBP (mmHg)	**163**	153	**0.01**
DBP (mmHg)	**91**	86	**0.032**
LVH on EKG (%)	**47.3**	35.8	**0.033**
Hypertension (%)	78.2	76.2	0.69
Atrial fibrillation on EKG (%)	13.6	17.7	0.379
Cholesterol (mg/dl)	207	204	0.659
Triglyceride	*106*	**137**	**<0.001**
Glucose (mg/dl)	*155*	**182**	**0.023**
History of Diabetes (%)	*20.9*	**36.9**	**0.001**
Platelet	*204*	**226**	**0.009**
White Blood Cell	**11666**	**9296**	**<0.001**
Current smoker(%)	13	13	0.97
Drink alcohol (%)	10.0	7.6	0.53
Complications after stroke (%)	**62.7**	**28.2**	**<0.001**
Death at discharge (%)	**34.5**	**6.1**	**<0.001**

Table 3. Odds Ratio (95% confidence interval) of hospital death among stroke patients

Variable	Over all OR (95% CI)	Ischemic OR (95% CI)	Hemorrhagic OR (95% CI)
Race (Chinese=1)	1.01 (0.70-1.40)	1.06 (0.50-3.10)	1.34 (0.81-2.12)
Gender (male=1)	1.60 (0.83-3.08)	1.36 (0.51-3.67)	2.17 (0.62-7.53)
Systolic BP (=30 mmHg)	**1.58 (1.36-1.78)**	**1.50 (1.11-3.05)**	**1.91 (1.42-3.46)**
Heart disease(yes=1)	**2.01 (1.02-4.19)**	2.17 (0.92-4.89)	0.98 (0.37-5.03)
Blood Sugar (=10mg/dL)	**1.27 (1.02-1.54)**	**1.54 (1.12-2.06)**	1.19 (0.76-1.82)
Diabetes (yes=1)	**2.64 (1.35-5.20)**	**3.02 (1.14-7.89)**	2.23 (0.46-19.98)
Cholesterol (=20mg/dL)	1.26 (0.97-1.59)	1.20 (0.88-1.61)	1.02 (0.69-1.95)
WBC(=1000 counts)	**1.26 (1.06-1.50)**	**1.20 (1.03-1.40)**	**1.32 (1.05-1.61)**
Type of stroke (Ischemic=1)	**5.43 (4.54-6.97)**		

Stroke Patients: Taipei vs. New York

Chinese stroke patients at National Taiwan University Hospital, Taipei and NYU Downtown Hospital were different. The age of *stroke onset was even younger in Taiwan* (cerebral infarction 65.5 y vs. 71.8; cerebral hemorrhage 58.2 y vs. 67.3). Incidence of cerebral hemorrhage was also higher in Taipei (30.2 vs. 23.4%). Patients at NYU Downtown Hospital had higher incident of hypertension, diabetes mellitus, atrial fibrillation, and higher cholesterol. The patients in National Taiwan University had higher incidence of smoking, drinking, higher triglycerides. Of importance is the *low incidence of carotid stenosis* at both cities. There were few patients with more than 50% carotid stenosis (11.9 vs. 10.9%), this may support the observation that Chinese stroke is more likely due to microvascular disease. The higher social acceptable alcohol and binge drinking habits in Taiwan may explain the higher incidence of cerebral hemorrhage and at a younger age.

The stroke patients' mortality rate was similar in both places (10.77 vs. 11.01%). Deaths from cerebral infarction was 5% in both places, however, case fatality from cerebral hemorrhage and subarachnoid hemorrhage was very high (21.74, 30.49%; 35.77, 33.85%).[6](table 4).

Table 4.

Differences of stroke risk factors between NTUH and NYUDTH stroke registries

	NTUH (n=2,285)	NYUDTH (n=427)	*p* value
Hypertension	63.9%	73.5%	0.0001
Diabetes mellitus	25.3%	30.0%	0.04
Atrial fibrillation	12.3%	17.6%	0.003
Ischemic heart disease	23.1%	22.7%	0.9
Smoking	32.6%	21.5%	0.0001
Drinking	22.1%	8.0%	0.0001
Left ventricular hypertrophy	35.1%	37.0%	0.4
Serum cholesterol ≥240 mg/dl	12.2%	20.0%	0.004
Serum triglyceride ≥200 mg/dl	27.1%	12.2%	0.0001
Serum uric acid ≥7.0 mg/dl	27.7%	32.6%	0.2
Carotid stenosis ≥50%	11.9%	10.9%	0.7

p value by Mantel-Haenszel x^2 test.

Blood Pressure control Manhattan Chinese Community vs. NHANES III

Compared with subjects in NHANES III, a surveyed to collect information about the health and diet of people in the United States between 1988 and 1994 including 40,000 people., We screened 911 residents in Chinatown, of the 752 valid study objects, many did not know they have hypertension(36,16,12,10% p<0.01).Not only less aware of their hypertension, those who know, their high blood pressure control is less than ideal compared to whites, blacks and Hispanics in the NHANES III (65,16,12,10% p<0.01).

The fact that the Chinese American patients *are less aware of their hypertension and blood pressure is less well controlled* suggest that stroke is but only a small tip of the health risk iceberg of the communities.[7]

The Diet and Stress Factors

Since September 2000, Dr. Jing Fang and I are conducting a case controlled study supported by American Heart Association, to determine the risk factors for stroke among foreign-born Chinese in New York City. The preliminary analysis of the patients admitted through January 31, 2002 is going to be presented at the coming American Epidemiology Society meeting. Questionnaire with detailed information including language, job, medical history and care, dietary pattern, smoking, exercise, as well as changes of these factors after immigration to US were interviewed among 84 hospital stroke cases (20 hemorrhagic stroke) and 74 age-matched hospital controls: Mean age were 73.8 and 74.0 years (p=0.732), with 45% and 48% men (p=0.23), and mean years after immigration to US are 24 and

27 (p=0.01) respectively. Stroke patients have higher blood pressure (135/72 vs. 163/84 mm Hg, p<0.001), more likely to have history of hypertension (52% vs. 67%, p=0.02), to be current smokers (8% vs. 25%, p=0.0125) with increased numbers of cigarettes consumed after immigrating to US. Although exercise during the past 12 months was similar between cases and controls, controls were more likely to participate exercise 20 years ago (43% vs. 27%, p=0.006), increased the amount of exercise after immigration to US (19% vs. 12%, p=0.032). In addition, controls were more likely to change their way of cooking, using less sugar and salt after immigration. Logistic regression analysis, controlling for other characteristics, showed that adjusting score was significantly related to stroke with odds ratio of 0.87 (0.74-0.99, p=0.05) favoring the case control. These results suggest that *increased stress* among Chinese immigrants in US is associated with the subsequent development of stroke. After immigrating to USA, controls also consume more Fish, soybean products and fruit juice than stroke patients.

Patients' response to onset of symptoms

We also look at patients' response to stroke symptoms. The charts of thirty-seven consecutive Chinese patients admitted to NYUDT Hospital between Dec 2000 to Aug 2001 were reviewed. Ten (27%) came to the ER within 3 hours of symptom onset, 8 (21.6%) between 3-6hr; 9 between 7-12 hr;10 between 2-7 days. Ten (27%) had brain CT taken within 1 hr after registration, 12 (32%) between 1-2 hr, 6 (16%) 2-3 hr, and 9 (24%) >3hr. Overall, 28 (76%) brain CT were completed within 3 hr and the median time was 92 min (range 2 min to 16 hr. Presuming other variables such as hypertension control, anticoagulation use, lab result, etc. are favorable, and half of those coming to the ER within 3hr can have a Brain CT in 1 hr, only **7%** of current Chinese stroke patients is eligible to be evaluated (not treated) for t-PA treatment. If improvments in patient education could make those presenting to ER within 4-6 hr of symptoms onset to the 3hr time frame, and if increased efficiency will shorten the time to get a CT scan from 3 to 1 hr. , we will increase patient eligibility to **37%**. This will increase t-PA usage, which has a new window of three hours, hopefullly will result in lesser patient long term disability and improve community health. [7]

Conclusions:

1. Chinese American IPA (CAIPA) and NYU Downtown hospital serve a unique, relatively rapid growing and graying Chinese American community at New York City.

2. There is a higher prevalence of stroke risk factors including untreated/uncontrolled hypertension, uncontrolled diabetes, heavy smoking, hyperlipidemia and physical inactivity.

3. Among Chinese stroke patients, there is an unacceptable higher risk for cerebral hemorrhage with increase mortality and disability.

4. Stroke is but only a small tip of the health risk iceberg of the communities. Medical education and prevention can minimize various risks factor for stroke and disease progression, e.g. Chinese patients are less aware of their blood pressure and their blood pressure is also less controlled.

5. Organized physician network such as CAIPA/CAMS can and should continue to champion the study of the unique health status of the Chinese community, which is largely neglected by the main stream research.

6. CAIPA/CAMS members is the key to promote/improve the health of the Chinese Community.

The above studies were partially supported by NYUDH Chinese Community Partnership for Health, Chinese American Medical Society (CAMS), the United Chinese Health Foundation, a grant from the National Science Council in Taiwan. Special thanks to Susan Lau, Cora Fung and Betty Chin for their invaluable assistance

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7. SH Foo, J Fang, C Fung. Potential Benefits of Tissue Plasminogen Activator in Treating Acute Brain Attack of Chinese Patients at NYU Downtown Hospital. Abstract. Chinese American Medical Society 2001 Annual Meeting, New York. Nov 17, 2001.

Sun-Hoo Foo, M.D .is Associate Professor of Neurology, New York University Medical School, and Director of Neurology, NYU Downtown Hospital.

Recent Advances in MRI Technology in the Diagnosis and Treatment of Ischemic Stroke

Chung Y. Hsu, M.D. Ph.D.

Diffusion weighted imaging (DWI) has been widely used to study patients with acute ischemic stroke. While DWI is highly sensitive in depicting an ischemic lesion, its value in predicting final infarct volume during the acute stage has been called into question. However, when coupled with perfusion weighted imaging (PWI), a mismatch has been suggested to delineate reversible ischemic lesions that may be amenable to therapeutic interventions.

DWI and PWI

- When mismatched defects are present between DWI and PWI defined lesion, the mismatched tissues indicate regions of ischemic pneumbra.
- In contrast, when PWI/DWI defied lesion is matched, no salvageable tissues are expected.

A number of clinical trials of neuroprotective agents are ongoing in the US and other countries applying DWI/PWI in the selection of patients with salvageable brain tissue. However, the lack of quantitative measurements for the perfusion-weighted images and the definitions of the ischemic lesions are somewhat subjective, making it difficult to consistently determine the ischemic lesions.

Therapeutic window

- t-PA is the only FDA-approved therapy proven to be effective in patients with acute ischemic stroke.
- Population studies indicate that the therapeutic window for t-PA is only 3 hours after symptom onset.
- This imposes a major limitation on the clinical utility of t-PA treatment (only 1-2% of patients are treated)

Individualization of treatment?

- However, it is likely that the therapeutic window varies between individuals, depending on:
  - Variations in vasculature between individuals.
  - Collateral flow pattern.
  - Comobidities, temperature, etc.
- With the availability of acute therapies, there is an increasing need for methods to define the viability of ischemic brain tissue so that acute therapies can be more appropriately offered to patients and therapeutic windows can be individualized.

Compensatory Mechanisms

- CBF reserve.
- CBF autoregulation:
  CBF = CP/CVR CPP = SAP - ICP
- Supply-demand balance (affected by O_2, CO_2, pH, Hct, neuronal activity, diseases of the arteries and others.
- Oxygen Extraction Fraction (OEF): 30-90%

Brain Oxygen Metabolism (CMRO2)

- Normal CMRO2 can be maintained at 50-65% of normal CBF.
- Decompensation → Subnormal CMRO2.
  1. After maximal vasodilation
  2. After maximizing OEF
  3. Increase in metabolic demand (e.g., increased neuronal activity caused by Glutamate release, increased energy consumption secondary to IEG expression, DNA repair, seizures, etc.)

PET : Limitations

- Advantages
  - "Gold standard" for imaging pneumbra (CMRO2)
- Disadvantages
  - Requires multiple radiotracers with very short half-lives.
  - In-house cyclotron is needed to generate these tracers.
  - Long acquisition times (tracers must reach equilibrium).
  - Requires arterial line (problem for patients receiving thrombolysis).
  - Low resolution (voxel size - 1 cc).

MRI : Limitations

- Advantages
  - Noninvasive.
  - Does not involve radiation.
  - Relatively rapid image acquisition.
  - High resolution.
- Disadvantages
  - DWI lesion does not necessarily represent irreversibly injured tissues, thus DWI/PWI mismatch does not represent pneumbra

Newer MR techniques are being developed to aid in the delineation of the dynamic pathophysiology of brain injury following ischemia. Novel MR sequences based on the BOLD mechanism are useful in the assessment of the extent of deoxygenation in ischemic tissue an adjacent areas to derive the oxygen extraction fraction (OEF). In addition, an absolute measurement of cerebral blood flow (CBF) can also be obtained. By combining both MR based CBF and OEF, metabolic rate for oxygen (CMRO2) may also be estimated.

Blood Oxygen-level dependent (BOLD) contrast

- Deoxyhemoglobin molecules behaves as paramagnetic particles which can induce local magnetic field changes.
- changes in the amount of deoxyhemoglobin will alter MR signal intensity in T2*-weighed images.

$$\text{MR-CMRO2} = \text{CBF} \times \text{OEF}$$
$$\text{OEF} = 1 - \text{CBOS}$$

From PET to MRI

- Can oxygen metabolism be measures by MRI?
- Blood oxygen-level dependent (BOLD) contrast
  - Deoxyhemoglobin molecules behave as paramagnetic particles which can induce local magnetic field changes.
  - Changes in the amount of oxyhemoglobin will alter MR signal intensity in T2*-weighed images = BOLD contrast

MR-CMRO2

- Cerebral oxygen saturation can be obtained with MRI.
- Assuming that the arterial blood is fully saturated (100%), OEF can be obtained as 1- CBOS

MR-CMRO2=CBFxOEF

Using MR-CMRO2 method, significant difference between core lesions that are destined for infraction vs. penumbra with viable brain tissue can be differentiated. Further advances in the development of MR-CMRO2 may obviate the need of PET scanners to measure CBF, OEF, and CMRO2, and may permit serial imaging to delineate the dynamic pathophysiology of brain ischemia. These MR- derived parameters may also supplement DWI/PWI in predicting the fate of acute ischemic lesions.

MR_CMRO$_2$ feasibility study in acute stroke patients - conclusions

- MR_CMRO$_2$ maps may reveal the viability of ischemic brain tissue.
- MR_CMRO$_2$ could potentially be utilized to identify the ischemic pueumbra and individualize therapeutic windows.
- The experimentally measured CMRO$_2$ threshold needs to be further evaluated in a larger sample size.

The visualization of water diffusion anisotropy in CNS white matters has made diffusion tensor imaging (DTI) a promising tool for non-invasive *in vivo* neuronal fiber tract mapping. This technique has been applied in human and animal brains for neuronal fiber tracking in three dimensions. DTI may be used to assess the extent of myelin formation or degradation. It carries the potential for differentiation of demyelination from the axonal injury. The DTI method has been used to assess myelin abnormalities in mice with genetic defects in white matter integrity. DTI may also be applied to define white matter injury in ischemic brain or traumatized spinal cord. DTI has greater sensitivity than conventional MR sequences in identifying acute or chronic white matter lesions, and is likely to be useful in the future to monitor the resolution or progression of white matter lesions caused by ischemia, trauma, or chronic neurodegenerative diseases.

Diffusion weighed MR Imaging

- Sensitive to tissue pathology.
- Early detection: stroke and tumor.
- complication: diffusion anisotrophy → misrepresentation of anatomy
- Advantage: diffusion anisotriphy → Diffusion Tensor Imaging (DTI)
- DTI: White matter tract tracking & quantitative analysis of white matter pathophysiology.

White matter injury in inflammation

- Inflammatory/immune reactions in CNS have a predilection to cause WHITE MATTER lesions.
- Inflammatory cells (PMN's, macrophages/microglia, and astroglia) and inflammatory mediators may play a more important role in the secondary injury to white matter.

Is white matter affected in Alzheimer's Disease?

- Amyloid peptides are cytotoxic to oligodendrocytes.
- Subcortical white matter lesions are common among patients with AD or cerebral amyloid angiopathy.
- Cerebral conduction delay has been documented in AD patients.

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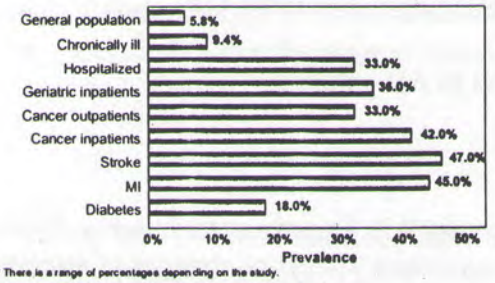
Cardiovascular Disease and Depression

Henry Chung, M.D.

(The following is the Power Point slides presentation of Dr. Chung's presentation)

Prevalence of Depressive Disorders in Various Patient Populations*

NEUROSCIENCE



* There is a range of percentages depending on the study.

Adapted from WPA/PTD Educational Program on Depressive Disorders
Gavard JA, et al. *Diabetes Care*, 1993, 1167-1178.

Fluoxetine vs. Nortriptyline in Patients with IHD

NEUROSCIENCE

- 7-week open label study of 27 patients on fluoxetine or nortriptyline
- Fluoxetine had no effect on cardiac conduction, ventricular arrhythmia, or orthostatic blood pressure
  - In contrast, nortriptyline caused a significant increase in heart rate and orthostatic hypotension
- Only 4% of fluoxetine patients experienced an adverse cardiovascular effect vs. 20% for nortriptyline patients
- Fluoxetine induced a 6% decrease in heart rate, a 2% increase in supine systolic pressure and a 7% increase in ejection fraction

Roose SP et al., *Am J Psych*, 1998;155:660-665

Does Comorbid Depression Alter Outcome of Physical Illness?

NEUROSCIENCE

- Depressed post-stroke patients
  - less compliant with treatment, more irritable and demanding, and have an apparent personality change (Ross and Rush, 1981)
- Depressed patients following MI
  - less compliant with rehabilitation programs and more likely to have protracted recoveries and slow return to normal functioning (Guiry E, et al., 1987)
- Depressed diabetic patients
  - poorer glucose control (Lustman PJ, et al, 1988)

Paroxetine vs. Nortriptyline in Patients with IHD

NEUROSCIENCE

- 6-week double-blind study of 81 patients on paroxetine or nortriptyline
- Paroxetine had no sustained effects on cardiac conduction, blood pressure, heart rate, or indexes of heart rate variability
  - In contrast, nortriptyline caused a significant increase in heart rate (11%) and a reduction in heart rate variability
- Only 2% of paroxetine patients experienced an adverse cardiovascular effect vs. 18% for nortriptyline patients
- Paroxetine and nortriptyline were both effective treatments for depression in these patients with IHD, although nortriptyline was associated with a significantly higher rate of serious adverse cardiac events

Roose SP et al., *Am J Psych*, 1998;155:660-665

Increased Mortality Associated with Depression and Physical Illness

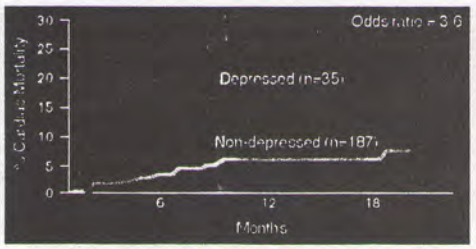
NEUROSCIENCE

- Murphy et al found in a prospective study of elderly patients that when the effect of physical illness was controlled for, depressed patients had a significantly higher 4-year mortality than nondepressed controls
- Silverstone found in a study of 211 hospitalized patients with a life-threatening illness that depression increased mortality
  - *Depressed patients had significantly poorer outcome over the 28 days following admission, with 47% of the depressed patients dying or having life-threatening complications as opposed to 10% of the nondepressed patients*

Murphy E, et al. *Brit J Psych*, 1988, 152:347-353.
Silverstone PH, *J Psychosomatic Res*. 1990, 34:6;651-657.

Major Depression Post MI – Impact on 18-month Survival

NEUROSCIENCE



Frasure-Smith & Lesperance. *Circulation*, 1995;908-1006

Previously Identified Risk Factors for Coronary Artery Disease

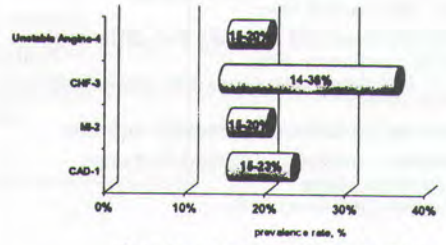
NEUROSCIENCE

- Genetic Factors
- Insulin Resistance
- Hypertension
- Thrombocyte Dysfunction
- Hyperlipidemia

Photograph: Davies MJ. Circulation. 1996;94:20 13-2020.

Prevalence Rates of Depression in Patients with Cardiovascular Illness

NEUROSCIENCE



1-Carney, 2-Schleifer, 1989; Ladwig, 1991; Frasure-Smith, 1995; 3-Jiang, 2001; Koenig, 1988; Frasure-Smith, 1993; 4-Lesperance, 2000)

Depression is a risk factor for the development of cardiovascular illness

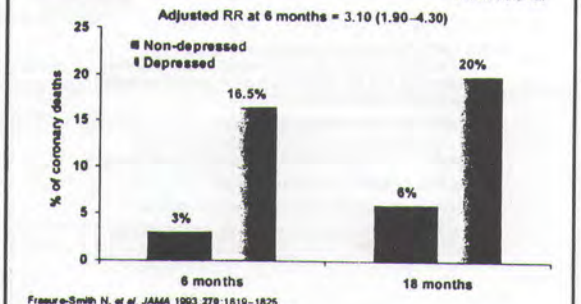
NEUROSCIENCE

- Multiple large-scale studies have prospectively followed healthy subjects
- Depression is a significant independent risk factor for CAD morbidity and mortality
- Adjusted relative risk: in range of 1.5 to 2-fold

(Ferketich, 2000; Ariyo, 2000; Schulz, 2000; Barefoot, 1996; Aromaa, 1994; Everson, 1996; Anda, 1993; Ford, 1998)

Six month and eighteen month coronary fatalities after acute MI

NEUROSCIENCE



Frasure-Smith N, *et al. JAMA* 1993;270:1819–1825.
Frasure-Smith N, *et al. Circulation* 1995;91:999–1005.

Depression increases risk in patients with existing CAD

NEUROSCIENCE

- Among individuals with established ischemic heart disease:
  - Depression contributes a 3-to-4 fold increase in the risk of subsequent cardiovascular morbidity and mortality

(Frasure-Smith, 1993 and 1995; Ladwig, 1991; Carney, 1988; Lesperance, 2000; Bush, 2001; Welin, 2000)

Minimal Symptoms of Depression Increase post-MI Mortality Risk

NEUROSCIENCE

- 285 post-MI patients were prospectively evaluated for symptoms of depression
- Multiple logistic regression revealed independent predictors of mortality were:
  - Age ≥ 65 years
  - LVEF <35%
  - Diabetes Mellitus
  - Any depression present at the time of AMI (DSM-IIIR or Beck Depression Inventory (BDI) score ≥10)
- Highest mortality rates were were observed in patients with most severe depressive symptoms
- However, compared with those without depression, *higher mortality was also observed at very low levels of depressive symptoms* (BDI 4 to 9) not generally considered clinically significant and below the level unusually considered predictive of increased post-MI mortality

Bush DE, *et al. Am J Cardiol* 2001;88:337-341.

Possible Mechanisms of CV Risk Associated With Depression

NEUROSCIENCE

- Increased platelet activation/aggregation
  (Nair, 1999; Nemeroff, 1993)
- Reduced heart rate variability and alterations in cardiac autonomic tone
  (Stein, 2000; Gorman, 2000; Carney, 1995; O'Connor, 2000; Carney 2001)
- Reduced compliance with medical regimens
- Reduced compliance with lifestyle change recommendations
  (Ziegelstein, 2000; Carney, 1995)

SADHART: Study Goals

NEUROSCIENCE

- STUDY GOALS
  - To investigate the cardiovascular safety, tolerability and antidepressant efficacy of sertraline treatment of depression in patients identified during hospitalization for acute myocardial infarction or unstable angina

O'Connor CM, et al. *Circulation* 2001; 140(17)-supplement

Enhancing Recovery in Coronary Heart Disease (ENRICHD) study intervention: rationale and design

NEUROSCIENCE

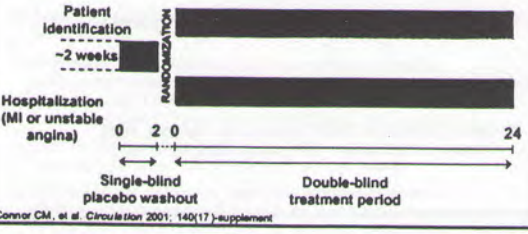
- The ENRICHD study is a multicenter, randomized, controlled clinical trial of a cognitive-behavioral treatment for depression and low social support in post-MI patients. A total of 2481 patients were recruited.
- Key features of the intervention include:
  - The integration of cognitive-behavioral and social learning approaches to the treatment of depression
  - Rapid initiation of treatment after MI
  - A combination of individual and group modalities
  - Adjunctive pharmacotherapy for severe or intractable depression

The ENRICHD Investigators, *Psychosomatic Medicine*. 63(5):747-55, 2001 Sep-Oct

SADHART: Study design

NEUROSCIENCE

- Multicenter study (USA, Canada, Australia, Denmark, Sweden, Italy, Germany)
- Target sample size: 600 patients
- Primary safety and clinical endpoints were obtained at week 16



O'Connor CM, et al. *Circulation* 2001; 140(17)-supplement

SADHART

Sertraline Anti-Depressant Heart Attack Randomized Trial

NEUROSCIENCE

SADHART: Inclusion Criteria

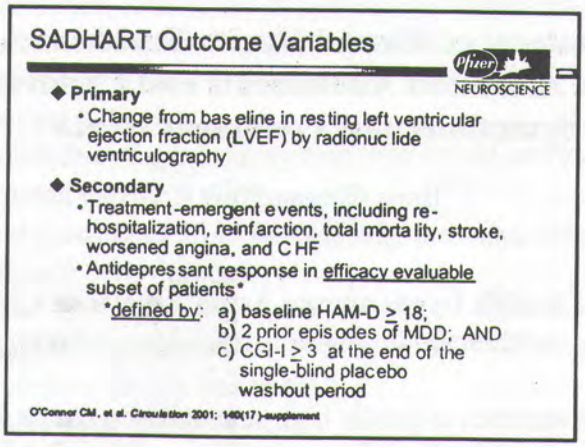
NEUROSCIENCE

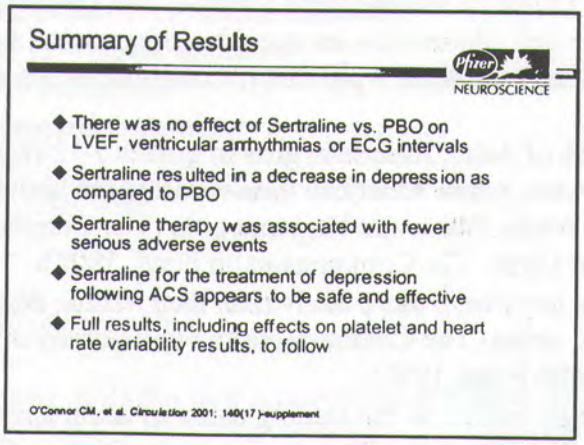
- Male or Female, aged 21 years or older
- In past 30 days meets criteria for a dual cardiac / psychiatric diagnosis:
  - Either acute MI **or** unstable angina (using stringent criteria)

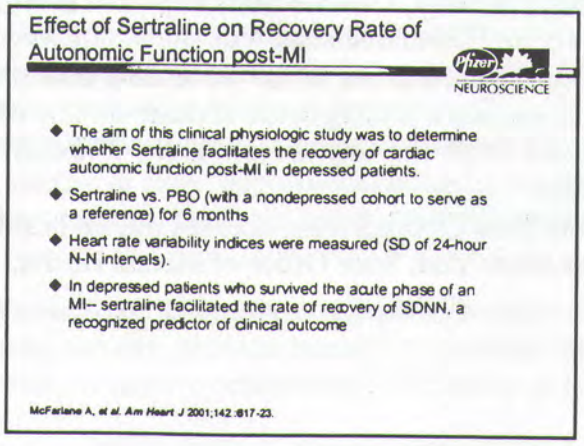
  and

  - Major depression (using DSM-IV criteria based on a structured interview)

O'Connor CM, et al. *Circulation* 2001; 140(17)-supplement







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The Prevalence of Mental Health Problems Among Asian American Adolescents and Children: Symptoms and Treatment Issues

Irene Chung, Ph.D.

A Statistical Profile of Mental Health Issues among Asian American Children and Adolescents:

- 96% of Asian American children are immigrants or children of immigrants (1996 Housing and Vacancy Survey).
- 33% of Asian American students in public high schools drop out or do not graduate on time (Class of 1999 Four Year Longitudinal Report and Event Drop Out Rates, NYC Board of Education).
- The number of Asian American youths arrested for major felonies increased 38% between 1993 and 1996 (NYPD, Office of Management Analysis and Planning).
- Asian American children and adolescents are considered by mental health providers to be highly prone to depression (Fact Sheet April 2001, Coalition for Asian American Children and Families).
- In a national survey, 30% of Asian American girls in grades 5-12 reported suffering from depressive symptoms. Also, Asian American girls reported the highest rates of depressive symptoms compared to White, Black and Hispanic girls (The Commonwealth Fund Survey of the Health of Adolescent Girls. The Commonwealth Fund, 1998).
- Asian American teenage boys were more likely than their White, Black and Hispanic peers to report physical or sexual abuse (The Commonwealth Fund Survey of the Health of Adolescent Boys. The Commonwealth Fund, 1998).
- In 1997, suicide alarmingly ranked as the leading cause of death among South Asians ages 15-24 in the U.S. (Monthly Vital Statistics Report. Center for Disease Control and Prevention/National Center for Health Statistics, Vol. 46, No. 1, Aug. 1997).
- Asian American women ages 15-24 have a higher rate of suicide than Whites, Blacks, and Hispanics in that age group (Monthly Vital Statistics Report. Center for Disease Control and Prevention/National Center for Health Statistics, Vol. 46, No. 1, Aug. 1997).
- In New York City in 1999, suicide was one of the ten leading causes of death for Asian Americans of all ages, but was not a leading cause of death for any other ethnic group (Summary of Vital Statistics 1999, The City of New York, Office of Vital Statistics, New York City Department of Health).
- Of all the children in New York City receiving licensed mental health services in 1995, only 1% was Asian Americans (New York State Office of Mental Health, 1995 Patient Characteristics Survey).

Mental health stressors for Asian American children and adolescents:
As minority members and descendants of immigrant families, there are many psychological burdens created by:

- the prevalence of racism in society
- the lack of Asian mentors in the school system who could serve as advocates and role models
- cultural and generational conflicts with parents
- the lack of emotional nurturance from parents who are often overworked and experience difficulties in adjusting to a new country.

Some debilitating conditions:

- verbal and physical abuse by parents
- sexual abuse by parents or family members
- scapegoating in school or at home
- prolonged separation from parents/placement with different caretakers during infancy and childhood

Depressive Disorders:

- Major Depressive Episode (6 – 9 month duration)
- Dysthymic Disorder (2 – 4 year duration)
- Transient Depressive symptoms

Anxiety Disorder as a comorbid condition:

- Separation Anxiety
- Generalized Anxiety Disorder
- Social Phobia
- Specific Phobia
- Obsessive Compulsive Disorder

Depressive symptoms among children and adolescents are often different from those observed among adults.

Behavioral and attachment symptoms are frequently observed among infants and children of very young ages who are physically or emotionally separated from their primary caretaker.
Examples with infants: whining during initial separation period with caretaker; after prolonged separation, symptoms may include impaired social interaction; slow motor responsiveness; dazed and immobile facial expression; slowed or stunted growth; susceptibility to infection.
Examples with toddlers: irritable moods; delays in developmental milestones such as walking, language, and toilet training; nightmares; self-stimulating behaviors (rocking, head banging, masturbation); clinginess; excessive fears; oppositional behavior; decrease in play.
Examples with pre-schoolers: sadness, tiredness, anger, apathy, irritability, social withdrawal, weight loss, motor retardation.

Cognitive and emotional symptoms are more common with older children and adolescents.
Examples with older children: anxiety, phobias, somatic complaints, reluctance to leave the room or house, complaints of boredom, disruptive behavior at home and/or at school, decline in academic performance.
Examples with adolescents: volatile mood, rage, intense self-consciousness, low self-esteem, poor academic performance, truancy, delinquent behaviors, substance abuse, sexual acting-out, social withdrawal (anhedonia), eating and sleep disturbance.

Cultural values and norms that may contribute to depressive symptoms/syndrome:

- Family is the central unit of life and one's sense of self and identity revolves around meeting family expectations and needs
- Total obedience and compliance toward authority and parental figures.
- Communication patterns that sanction internalization of negative feelings and indirect expression of love.
- Academic achievement of children perceived as validation of parents as "good" parents, and the pathway to a successful life for the children

Suicidal Risk Factors:

- Poor problem-solving and coping skills in handling disappointments and losses in life
- Difficulties in managing or expressing anger
- Isolation in family and school
- Dysfunctional family environment
- Family history of suicide/ suicidal attempts/ suicidal threats
- Family history of loss of loved ones and views of death and dying

Suicidal Risk Symptoms:

- Accident-prone behavior (children)
- Preoccupation with death and morbid thoughts (children)
- Self-hate ideations
- Inability to recover from relationship breakups (adolescents)
- Fascination and identification with icons who embrace the idea of "death" (adolescents)

Recommended Treatment approach:
Combination of individual and family therapy
Use of culturally sensitive interventions:

- Family-syntonic approaches versus blaming parents, i.e., reframing generational conflicts to project a sense of hope for the family; validating the hardships and aggravations of the parents.
- Role-modeling parenting techniques that are culturally meaningful, i.e., some discipline and goal-setting; a balanced focus on outcome.
- Cognitive and behavioral approaches in working with the individual child/adolescent to improve self-esteem and coping skills.
- Facilitating communication of positive feelings between parents and child.

Medication to alleviate/stabilize more severe symptoms

Treatment Issues:

- Parents' perception of problem: child is being "lazy", "defiant", etc;
- Parents' perception of solution: child needs to develop better will power, get closer supervision, spend more time at home, etc.
- Parents find it difficult to understand the concepts of "blanking out", "lack of motivation and concentration", "anger outbursts" as depressive and anxiety symptoms.
- The lack of commitment to seek mental health treatment because of the stigma associated with mental illness, and the lack of understanding of the goals and means of psychotherapy.

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Abstract # 1

BREAST CANCER SCREENING AND CANCER SUPPORT SERVICES IN THE CHINESE COMMUNITY Lei-Chun Fung, MPH, MSW and Jennie Woo, PHN, MPH, Chinatown Public Health Center, San Francisco Department of Public Health, 1490 Mason Street, San Francisco, CA 94133

Chinese Americans make up the largest Asian American Group in the Bay Area; and among this population, cancer is the second leading cause of death. Knowledge and support are vital components in helping people with cancer take charge of their experience. Yet, language and access barriers have hindered the monolingual Chinese speaking community from gaining access to screening program and support services that are available to the general public. Cultural beliefs, fear, and isolation also hinder Chinese speaking women with cancer from facing and coping with the disease in an open manner. How would cancer screening, cancer support groups and cancer support services be received by monolingual Chinese speaking women in the community?

These programs will be highlighted through a poster presentation. (1) A model for developing a breast and cervical cancer prevention, detection and screening program through a collaborative outreach campaign using media, public and private clinics culminating in a Breast Health Day. (2) A model for planning and implementing a cultural relevant and successful Chinese Women's Cancer Support Group. Both Western and Eastern healing modalities were used in the support group and were very well received by the women in the group. (3) A support group called "Dr Play" for children whose family members are coping with cancer. The group uses art, play and sand to assist children in self-expression. "Dr Play" helps children to develop a deeper sense of self and more comfort participating in daily life. (4) Support services were developed to provide breast form fittings, wig styling and skin care services for Chinese women who had breast surgery or lost their hair while undergoing chemotherapy.

The presentation will highlight the various public and private collaborators in the planning and implementation of these programs. It will provide a better understanding of the physical and emotional needs of Chinese speaking women, effective strategies in providing appropriate and successful services, lessons learned and replication of models in other Asian Pacific Islander communities.

Abstract # 2

CCPH COMMUNITY HEALTH SCREENING IN MANHATTAN CHINATOWN JAN-JUNE 2001

Sun-Hoo Foo, MD[1, 3] Jing Fang, MD[2], Henrietta Ho-Asjoe[3], WaiWah Chung, RN[3]
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[2]Epidemiology and Social Medicine, Albert Einstein College of Medicine
[3]NYU Downtown Hospital and Chinese Community Partnership for Health (CCPH)

CCPH has routinely performed health screening in adjacent Chinatown since 1993. Health screening is usually done in the morning, subjects were advised in advance not to eat, and blood were sampled from finger sticks after interview or 2 hr post-prandial to measure glucose and cholesterol levels, using AccuData GTS Plus and Accu-Chek Instant Plus by Roche Diagnostic. Between Jan to June 2001, 911 community residents were screened. 9%(87) were between 25-44 year-old, 44%(409) were 45-64 and finger sticks were performed Y, and 45%(416) were >=65 Y. With increasing **age**, there are statistical significant rise in Cholesterol, Glucose and Blood Pressure (BP) level for those age <44 Y vs. >45 Y. (Age 25-44 vs. 45-64 vs.>=65: Cholesterol* 199.6, 207.6, 203.7 mg/dl; Glucose* 96.0,102.1,102.1, BP*13.9/77.1, 126.4/81.2, 136.5/79.6). These trends are similar to those reported by Howard Huey, MD, CCPH, et al. at the same community in Year 1993-4 (593 patients). However, comparing with their result, our population has higher BP, Cholesterol levels but lower blood glucose. This may suggest a changing diet habit, although the data can not be statistically compared.

Among other different subgroups in our survey, the followings are found also to be statistical significant. **Male** had lower mean cholesterol* (197.8 vs. 208.8 mg/dl), but higher mean glucose* (104.8 vs. 99.2 mg/dl), higher both systolic and diastolic BP (131.7/80.6 vs. 127.8/79.6 mmHg). 64%(581) had **no health insurance**, but they had lower systolic BP*(125.9/79.8 vs. 135.2/80.3). 63%(574) had **no PCP**, yet they also had lower systolic pressure* (125.7/79.5 vs.135.3/80.9). Significance of these is not clear.

393 **(43%)** residents had ***Cholesterol level >=200mg/dl***, especially in Female* (49% vs. 33% male) and older age group* (31%, 48% vs.40%). 192 **(21%)** had **Glucose level >=110** (male* 26% vs. female 19%). And 107 **(12%)** had **Glucose > 126 mg/dl** (male = female 12%). Significant number of older generation*(17%, 20% vs.23%) had glucose level >126mg/dl. 304 **(33%)** had **Blood pressure >= 140/90 mmHg**. Male*(39% vs.30% female), older age group*(13%, 32% vs.40%) have higher incidence of increased BP.

Our population was **not very aware of their health** status. Only 3.1%(28), 1.3%(12), 0.6%(6) stated that they had history of Hypertension, Diabetes mellitus or Hyperlipidemia. Yet **of those who denied the history, 33%(289), 20%(188), 43%(391) had clinical hypertension, hyperglycemia and hypercholesterolemia.**

Conclusion: There is still a significant high prevalence of hypertension, increased serum cholesterol and glucose levels, with increasing risk after age 45, among Chinese American residents in NYC Chinatown. This is similar to our earlier screening in 1993-5 but suggests a trend towards increasing BP and Cholesterol but lower Glucose level. The most important findings are the unawareness and the high prevalence of having these common, treatable but dangerous risk factors. Although further analyses and studies are required, these facts underscore the importance of continue health education and preventive measure in improving the community health.

*p<0.01, others<0.05.

Abstract # 3

A Follow up report on the Community-Wide Diabetic Screening in Chinese Community in NYC in 2001. George Liu, CAIPA, Christopher Law, Oxford Health Plan, Alan Tso, Jian Qun Huang, Carol Chen, Charles B. Wang Community Health Center, Inc. New York, NY 10013

Background: The incidence of Diabetes Mellitus (DM) is increasing in the general population. American Diabetic Association (ADA) has modified its guidelines for screening and for the diagnosis of DM in recent years. In the general population, type 2 DM has been associated with obesity. However, there is little information on this important disease in the Chinese community. Last year we reported the preliminary data on BMI and the prevalence of abnormal blood glucose in this population. We have completed our data collection this spring. Our goals are to estimate the prevalence of DM by age, country of origin, years in the US, gender and family history.

Method: From 5/1/01 to 9/1/01, CAIPA, Charles B. Wang Community Health Center and Oxford Health Plan with the support of Aventis Pharmaceutical, embarked in a community wide screening for DM. Using the guidelines established by the ADA (fasting BS > 126mg/dl; non-fasting BS > 200mg/dl) we screened 2997 people. Last year, using this criteria; we reported that the prevalence was 6.5%. To obtain a better estimation of the prevalence of DM, we included the group of patients with history of diabetes with normal blood glucose.

Result: The number of Asian patients screened was 2997. 469 people were previously diagnosed with DM. 88 people had abnormally elevated glucose level but did not report any history of DM. In total, 557 of 2997 (18.6%) were found to have history of DM or were unaware of their elevated blood glucose level. The prevalence of DM is highest (30%) in the age group between 70 and 75. Of the 2338 born in China, 472 (20.2%) had DM. For those born in Hong Kong (n=191) and Taiwan (n=252), DM prevalence was reported to be 9.9% and 10.9% respectively. The group that has been in the US for 25-30 years was found to have the highest prevalence of DM (27.8%). 555 people reported family history of DM and 30.1% of them have been diagnosed with DM. Prevalence of DM in the male gender is 22% while females show a prevalence of 17%.

Conclusion: DM is an important disease in the Chinese Community. Previously we reported the prevalence of patients with abnormal blood glucose was 6.5%. When we included the 346 people with the history of DM with normal blood glucose levels the prevalence of DM became 18.6%. Furthermore, an estimated 16% of them did not suspect their diabetic status. The assessment of the risk factors shows positive correlations of DM with the increase of age, being born in China, positive family history, number of years one has been in the US and the male gender. We have established a database for this group of diabetic patients. Further studies, such as metabolic syndrome, with this group may give valuable insight into the management of DM.

Abstract # 4

BARRIERS TO DIAGNOSIS AND TREATMENT OF OSTEOPOROSIS IN CHINESE AND HISPANIC WOMEN. R Babbar MD, CM Lo MD, A Handa MD, S Guttmacher Ph.D, W Chung RN, C Fong RN, H Ho-Asjoe MPS, R Chan-Ting DO, NYU Downtown Hospital, New York, NY 10038

Background: Osteoporosis is a disease reaching epidemic proportions in the elderly population. Currently, an estimated 10 million Americans suffer from Osteoporosis and another 18 million have low bone mass, putting them at risk for pain and debilitation of fracture. No data exists about the prevalence of osteoporosis among Chinese women living in the United States. Currently, there are no data regarding the knowledge and awareness of osteoporosis among Chinese and Hispanic women.

Objective: Document the Level of community awareness. Document the prevalence of osteoporosis in this population. Define cultural barriers of this population to osteoporosis awareness. Identify barriers to access to treatment.

Design: The sample existed of immigrant women living in the Lower East Side of NYC, who are largely low-income Chinese and Hispanic, who volunteered to be screened, diagnosed and referred for care during a one-year period (2000-2001).

Analysis: Data was analyzed using parametric and nonparametric statistical methods.

Participants: Total 420 postmenopausal women, of which 300 were Chinese and 120 Hispanic.

Measurements: Questionnaire evaluating risk factors, knowledge, access, medical treatment of osteoporosis, and BMI. Calcium intake was calculated. Dexa Scan was done to evaluate the spine and hip for osteoporosis.

Results: Over half of the Chinese women (54 %) and over a quarter of the Hispanic women (26%) participating in the study were found to have osteoporosis. Only a small percentage of the Chinese women (7%) and more than a quarter of the Hispanic women (29%) had normal bone density. Both groups were noted to have concordance between education level, and calcium intake. The Chinese scored lower on osteoporosis knowledge questionnaire 15.73 verses Hispanic women 17.46. (sig. 003). Approximately half the women in both groups believe they are at risk for osteoporosis. Noticeably, more Hispanic women (58%) were willing to pay $50 to be screened for osteoporosis verses 14% Chinese. Education was highly correlated with knowledge score and calcium intake among both groups. Body mass index was highly correlated with level of osteoporosis in both groups. Only one third of both groups stated that their doctor had discussed osteoporosis with them. Half of the Chinese (50%) and a third of the Hispanic women (37%) were taking calcium supplementation. Only 2% of the population was being treated with medication for osteoporosis.

Conclusion: An epidemic of undiagnosed osteoporosis exists among the Chinese and Hispanic women of the Lower East Side of NYC. This population has limited knowledge and awareness about this disease. Two thirds them state that their physicians have not discussed osteoporosis with them. Significant outreach efforts need to be implemented to elucidate the problem further.

Abstract # 5

WOMEN'S HEALTH DAY: MEETING THE NEEDS OF THE CHINESE COMMUNITY

ANGELA SUN, MPH AND EDWARD A. CHOW, MD
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Women health issues have become an important aspect of health education in the past several years. This is particularly true in minority populations. To respond to this need, the Chinese Community Health Resource Center (CCHRC) with major sponsorship from the Chinese Community Health Plan, Susan G. Komen Breast Cancer Foundation, Chinese Hospital and pharmaceutical companies created a Women's Health Day in 1999. It was first of its kind in the Chinese Community. The health day was a collaborative project involving CCHRC, Chinese faith communities, and grass root community agencies targeting monolingual Chinese (Cantonese-speaking) women residing in San Francisco. The purpose of the project was to provide health educational opportunities to monolingual Chinese-speaking women, who cannot benefit from health educational opportunities offered in English. The Women's Health Day emphasized on wellness, prevention and health promotion and was free to all participants. The format of the event was a combination of seminars and health screenings. There was also free clinical breast examinations and assistance with enrollment of various free mammography programs since many of our targeted women have no health insurance coverage. The *Women's Health Data Book* by the Henry Kaiser Family Foundation and Jacobs Institute of Women's Health indicated that in the United States 24% of Asian Pacific Islander (API) women are without health insurance coverage. This factor is associated with poorer health status and barriers to health information and health care. At the Third Annual Women's Day, 30% of those surveyed had no health insurance coverage and 40% had household income below $20,000. Forty six percent indicated that the Women's Day was the only opportunity to receive health information in their language. During the Second and Third Annual Health Days, over 120 clinical breast exams were performed and mammograms were ordered for those who have no health insurance and have not had a mammogram within a year. Four patients were identified with possible breast cancer, of which all cases were diagnosed at an earlier stage (Stages II & I). The three Women's Health Days drew over 1600 Chinese women from various districts of San Francisco. Participants were asked to complete a program evaluation prior to leaving the facility. Fifty nine percent of the participants completed the evaluation; 65% rated the Health Day as above average. As a strategy to promote men's health, a special bonus program on men's health was also offered at each health day, and over 100 individuals participated in the men's health program each year. At the third annual (2001) Health Day, participants were also asked to complete a survey regarding their health practice. Of the 475 returned surveys, 35% had not been tested for Hepatitis B and 12% had family members tested positive for Hepatitis B; 50% had not been tested for diabetes and 23% had family members diagnosed with diabetes; 56% had not been screened for osteoporosis and 20% had family members diagnosed with osteoporosis; 25% had never had a mammogram, 15% never had a clinical breast examination and 43% did not perform breast self-exam regularly. These responses indicate the need for additional educational efforts and health screenings in future programs.

Abstract # 6

HEPATITIS B EDUCATION, AWARENESS AND SCREENING PROGRAM

David F. Der, M.D., Wayne Leong, M.D., David Law, M.D. Chinese American Physicians' Society, 817 HARRISON STREET, OAKLAND CA 94607

The Chinese American Physicians' Society of Oakland, California started a hepatitis B program in year 2001. The program was made possible by a grant from GlaxoSmithKline. This program consisted of three objectives. The first was to educate health providers on hepatitis B disease and its ultimate consequences, and the high incidence in the Asian American population. This objective was accomplished with 4 educational seminars for the health providers. The second objective is to bring awareness and information to the public regarding this disease. This objective was fulfilled through mass media communications, brochures, publicity and six public presentations. City officials, county supervisors and state legislators in the area were also informed of this program. The third objective was to provide free screening test for the public over the age of 18 years. The screening test consisted of an initial HBsAg. If this initial HBsAg was positive, there would be further testing for HbeAg and ALT level. There were 605 people tested in year 2001. Fifty-four people, or 9%, were found to be hepatitis B carrier (HBsAg positive). In this group, 7 people, or 13%, were found to be HBeAg positive, which suggested viral replication activity. Three of these seven people had high levels of ALT, which indicated hepatic degeneration or inflammation. Those subjects who were HBeAg positive were referred for further medical consultation and possible treatment.

Abstract # 7

B WISE PROJECT: RAISING AWARENESS AND EFFECTING TREATMENT OF HEPATITIS B IN THE SAN FRANCISO CHINESE COMMUNITY

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The Asian American and Pacific Islander community constitutes approximately 11% of California's total population and 21-31% of the total populace in the San Francisco Bay Area. Studies have shown rates of chronic hepatitis are highest among foreign born Asian and Pacific Islanders, particularly those originating from China and Southeast Asia. With 80% of California's Asian and Pacific Islander community being foreign born attention should be given to the disparate presence of the Hepatitis B virus afflicting this group. Though the prevalence of Hepatitis B virus carriers in the general U.S. population range from 0.1%-0.2%, a recent study published in the Asian American and Pacific Islander Journal of Health shows the incidence of HBV carriers among the Chinese and Southeast Asians ranges from 9% to 15%. The Chinese Community Health Care Association, (the IPA affiliated with Chinese Hospital) in partnership with the NICOS Chinese Health Coalition, a partnership of public and private San Francisco agencies serving the community, and the National Caner Institute sponsored Chinese Council of the Asian American Network for Cancer Awareness Research and Training (AANCART), with partial sponsorship from the GlaxoSmithKline Pharmaceutical Company implemented a comprehensive campaign in 2001 to address the pervasiveness of the Hepatitis B virus in the Chinese community. The project began in the summer with a lecture by Dr. Gary Euler, from the National Immunization Program of the Centers for Disease Control, to the Chinese community physicians on the need for adolescent Hepatitis B immunization. In the fall, over 100 providers from throughout the San Francisco community met to focus on preventive measures and early detection of possible carriers. This featured a lecture from the chair of the National Task Force of Hepatitis B Awareness on Asian Pacific Islanders, Dr. Son Do of Dallas, Texas. The meeting identified the need for more clarity for follow up guidelines once a patient was determined to be HBV positive. A subsequent panel of specialists and practitioners was convened to cull the information from the first provider meeting and create community specific guidelines for the detection and follow up of Hepatitis B carriers, and treatment of Hepatitis B patients in San Francisco. A comprehensive set of guidelines is due to be released in mid May 2002 to medical professionals in the Bay Area and will also be submitted to other Glaxo sponsored and national AANCART sites for review in the hopes they can be adapted to meet the needs of other communities. Bilingual educational workshops were also offered to the Chinese population outlining modes of transmission, treatment options, preventative measures and vaccination information. A total of 383 free Hepatitis B screenings were also carried out at various sites in the city to identify silent chronic carriers. The consumer screenings returned positive results for the Hepatitis B virus in 10.7% of the participants. The efforts of this coalition of organizations clearly illustrate the effectiveness of collaboration between agencies addressing a single topic in depth on behalf of the community. Moreover, the B-Wise project reminds us of the varying needs of distinct subsets within the overall populace. In celebrating the cultural diversity that is the United States we need to consider the uniqueness and differentiation of medical needs among the many races in the country as well.

Abstract # 8

A RETROSPECTIVE STUDY OF LAMIVUDINE ON CHRONIC HEPATITIS B – A COMMUNITY EXPERIENCE **Chien Chiang M.D., Katherine Chiang,**
St. Vincent's Hospital and Medical Center, New York, NY 10011

BACKGROUND - Lamivudine 100mg therapy has been shown to have biochemical, virological and histological benefits. The data on the optimum dosage is still lacking.

METHODS - Retrospective community study of 59 patients with chronic hepatitis B, treated with 150mg of Lamivudine for one year. Charts were reviewed to determine sex, age, liver enzymes, hepatitis B serology, and HBV-DNA levels. Results were compared to recent studies.

RESULTS - Of the 59 patients reviewed, 38 were included in the analysis. Patients were divided into two major groups. Classical group (HBeAG positive) 26 patients, and Precore Mutant group (HBeAG negative) 12 patients. In the classical group, the percent of HBeAG seroconversion (loss of HBeAG and the development of antibody to HBeAG) was 34%, ALT (alanine aminotransferase) normalization was 85%, and undetectable HB-DNA was 71%. In the precore mutant group, the ALT normalization rate was 83%, and 67% with undetectable DNA.

Chronic Hepatitis B – Classical Type

	Dienstag	**Lai**	**Chiang**
	100mg x 52wk	100mg x 52wk	150mg x 52wk
Lamivudine treatment			
Undetectable DNA	44%	98%	71%
ALT normalization	41%	72%	85%
HbeAG conversion	32%	16%	34%

Chronic Hepatitis B – Precore Mutant Type

	Tassopoulos	**Hadziyannis**	**Chiang**
	100mg x 52wk	150mg x 52wk	150mg x 52wk
Lamivudine treatment			
Undetectable DNA	63%	68%	67%
ALT normalization	63%	96%	83%

CONCLUSIONS - Lamivudine therapy shows biochemical and virological improvement in chronic Hepatitis B patients for both classical group and the precore mutant subset. The higher Lamivudine dosage does not improve HBeAG seroconversion or loss of DNA levels. Both groups show similar ALT normalization rate and DNA suppression. Lamivudine 150mg therapy results in a better ALT normalization rate as compared to Lamivudine 100mg for both groups. It is not clear if higher rates of ALT normalization will result in better histologic and clinical outcomes. Long term studies are needed. This higher dose is equal to the lower dose in DNA and HBeAG conversions and has no increased side effects. A dose of 150mg should be considered as a starting point in future combination (Adefovir and Epivir) studies.

Abstract # 9

A needs assessment to identify psychoeducational concerns of Asian Americans with lupus: Can a peer volunteer program work? Suzy Kim [1], Roberta Horton [1], Susan Flics [1], Enid Engelhard[2] and Stephen A. Paget[1].
[1], Hospital for Special Surgery, New York, NY
[2], The S.L.E. Foundation, Inc., New York, NY

Despite Asians being diagnosed with lupus 2:1 as compared with whites and being the fastest growing population (along with Latinos) in the US, little is published on psychoeducational needs of Asian-Americans with lupus. At past ARHP meetings, we reported on expansion initiatives to new populations of our two peer support/education programs, LupusLine and Charla de Lupus, yet few Asians have utilized these programs. A recent increase in Asian referrals led us to conduct a needs assessment to identify psychoeducational concerns in this community, with the goal to develop a culturally relevant intervention, if indicated.

Following a literature review, we designed structured questionnaires for both health care providers and Asian lupus patients as part of an interview process. The provider questionnaire (30 items) focused on doctor-patient communication, disease understanding/treatment adherence, and assessment of educational/support needs. The patient questionnaire (17 items) addressed acculturation, understanding of lupus/treatment, barriers to care and helpful interventions.

Major themes were: conflict between complementary and Western treatment modalities; fertility concerns; perception of physicians as authority figures; lack of educational material in their own language; burden on family, and social/cultural stigma related to illness. Patients expressed a desire to connect with a peer who "looks like them" and shares the same language/culture.

Due to the diversity of cultures within Asian communities, we recognized the importance of targeting outreach to one specific group. Our study demographics, city population statistics, and available community resources lead us to target our outreach to the Chinese community. Based on our needs assessment, LupusLine has partnered with a Chinatown-based health clinic, recruited bilingual volunteers with lupus and developed Chinese language materials. ARHP members interested in implementing programs for Asian Americans may find our presentation useful.

Disclosure: Programs supported by Rheuminations, Inc. and the United Hospital Fund.

Abstract # 10

The Emotional Distress in the Chinatown Community Following the September 11th Terrorist Attack.

Teddy Chen, CSW, Lin Fang, CSW, Jian-Ping Chen, MD, Ph.D.,
Hongtu Chen, Ph.D. Charles B. Wang Community Health Center, New York, NY 10013

Objectives: To examine psychological impact of the September 11th disaster on the immediate neighborhood of the New York World Trade Center.

Method: A total of 555 residents from the local Chinatown community participated in the study. Using a cross-sectional survey with a retrospective design, a questionnaire was administrated during approximately the fifth month after the disaster happened. The items about emotional distress were typical psychiatric symptoms of depressive disorders and anxiety disorders based on the DSM-IV criteria. About 88 percent of respondents completed and returned the questionnaires. All those endorsed symptoms of emotional distress were offer for further psychiatric evaluation at the local community health center.

Results: During the first two weeks immediately following the disaster, 59% of the people had four or more symptoms indicating near pathological levels of emotional distress. This number dropped to 17% five months after the disaster. However, More than half of the community residents had persistently shown one or more symptoms of emotional distress. Those who had lost a family member or friend in the disaster showed significantly higher distress, with 90% of them had four or more major psychiatric symptoms during the first few weeks right after the disaster, and the rate dropped to 35% five months later. Overall, those in their 40s and 50s seemed to have had relatively higher emotional distress than both younger and older groups. No gender differences were found.

Conclusion: Emotional distress was prevalent among the Chinatown residents in lower Manhattan right after 9/11. It was more devastating for those who lost family members or friends. A lot of residents are still severely affected 5 month later. Despite the persistent impact of the devastating trauma, the mental health condition of the community continues to recover.

Abstract # 11

TRADITIONAL CHINESE MEDICINE (TCM) AWARENESS: AN ASSESSMENT OF ALLOPATHIC PRACTITIONERS IN A METROPOLITAN SETTING. Leung R.C. M.D. [1], Kang-Yum E. RPH. , CSPI [2], Licht W. M.D. [1]
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[2] Consultant, Long Island Poison Control Center, East Meadow, New York

Background: Traditional Chinese Medical practice include modalities like, medication, acupuncture, pressure point message, the practice of Qi or Chi and many others. The effectiveness is proven by the proposition of the Chinese as a civilization. More recently, TCM has been incorporated into the treatment regime of Allopathic medicine, e.g. Artemisinin and Arsenic. America has a significant proportion of Chinese immigrants and the practice of Traditional Chinese Medicine is continued. These Chinese are also being treated in the Allopathic system in hospitals and clinics around where they live. There is a wide choice of Chinese Patent Medication, Traditional Chinese Medication and herbal foodstuff available to the Chinese in the US. There have been many reports of significant adverse clinical outcomes due to the administration of TCM in the Allopathic literature. However, there is little data reporting the incidence of such interactions in Allopathic practitioners. ***Method:*** An anonymous questionnaire was distributed amongst practitioners who work in the New York Downtown Area which has the highest concentration of Chinese living in the USA. The responders came from the Department of Internal Medicine NYU Downtown Hospital and the Chinatown Health Clinic. ***Results:*** A total of 51 surveys were returned. 86% were from Internal Medicine physicians and 78% were from the Residency training program. 67% of the responders routinely ask about the use of TCM in their clinical drug history and 76% of the responders reported experience in dealing with clinically significant adverse effects from TCM. Derangement of liver function tests was by far the most often cited outcome. The most often reported problem in dealing with these clinical events was the lack of information regarding the active ingredients. ***Conclusion:*** This survey reports an alarming incidence of adverse clinical reaction resulting from the use of TCM. The level of awareness is high amongst the responders demonstrated by the small 10% difference between the routine surveying of TCM use in history taking and in reported adverse outcomes. Effective management of such interaction is hampered by the lack of information regarding the suspected TCM. Definitive diagnosis is therefore difficult and impairs the reporting of such clinical events. In conclusion there is a great need for better documentation of active ingredients in TCM to ensure the safe administration of such agents to the general public.

Abstract # 12

THE PREVELANCE, USAGE OF TRADITIONAL CHINESE MEDICINE IN NEW YORK CITY'S CHINESE POPULATION Clifton Lee, Medical Student, Sophie Davis School of Biomedical Education, 223-44 56th Ave. Bayside NY, 11364

In New York City's Chinatown, Traditional Chinese Medicine coexists with Western Medicine. The purpose of this pilot study was to investigate this pluralistic medical system. It was a two-part study, which included open-ended interviews with practitioners, and a self-administered survey. 2 two practitioners were interviewed and a total of 55 survey responses were collected. The data found indicates that Chinese generally utilize the Western medical system, but are more familiar with the Traditional Chinese paradigm. The usage of Traditional Chinese Medicine also differs by ailment, financial status, origin, and acculturation into western society. Although the majority of the population surveyed preferred western medicine over Chinese medicine, there was still a significant portion that would prefer Traditional Chinese Medicine for the treatment of colds, dizziness, stomachaches, and broken limbs (26%, 24%, 21%, and 18% respectively). A cross-tabulation of fields showed that respondents who were Buddhist, from Mainland China, or recent immigrants, were more likely to use the alternative therapies. Also notable is that 66% of respondents reported that they felt that Traditional Chinese Medicine was less expensive than western medicine, even though 66% were covered by health insurance. This information suggests that although the majority of the population surveyed does not use Traditional Chinese Medicine, it still does have a significant presence in the community.

Abstract # 13

METABOLIC SYNDROME AND CORONARY ARTERY DISEASE IN THE CHINESE POPULATION OF NEW YORK CITY. Aung Z. Min, M.D, Tak W. Kwan, M.D, Luther T. Clark, M.D. SUNY Downstate Medical Center, Cardiology Department, 450 Clarkson Avenue, Brooklyn, NY 11203.

INTRODUCTION: The metabolic syndrome (MS) is a risk factor cluster that identifies patients at high risk for coronary heart disease (CHD). However, the relationship of the metabolic syndrome risk factor cluster to the presence and severity of CHD in Asian Chinese has not been defined. The objective of this study was to analyze the correlation of abnormalities associated with the metabolic syndrome with angiographically determined coronary artery disease (CAD) in a population of Asian Chinese undergoing cardiac catheterization for suspected CAD.

METHODS: We analyzed the relationship of angiographic CAD (more than 50% occlusion of coronary artery) with the abnormalities of the metabolic syndrome (present of at least 3 of following risks; Obesity with BMI of >30, Blood pressure >130/85, Serum glucose >110mg/dl, Serum triglycerides >150mg/dl, High-density lipoprotein <40 mg/dl in men and <50 mg/dl in women) in 239 Asian Chinese patients undergoing cardiac cath for suspected CAD. Normal coronary (0% occlusion) and not normal but no CAD (<50% occlusion) was also determined.

RESULTS: The study group comprised 239 patients, 58% (138) males and 42% (101) female with mean ages of 65 years and 72 years respectively. 77% (183) of patients had hypertension (HTN), 34% (81) smoking, 55% (132) high cholesterol, 27% (65) diabetes mellitus (DM), 13% (32) family history of CAD and (10) 4% peripheral vascular disease (PVD). 17% (30) of Non-DM patients had at least two and 16% (28) had at least three of the metabolic syndrome risk factors. 27% (65) of patients had previously diagnosed diabetes. When analyzed according to the presence or absence of angiographic CAD, 69% (45) of patients with diabetes, 61% (17) of patients with metabolic syndrome and 55% (80) of patients without MS or DM had CAD. Multiple vessels CAD was more common in patient with DM and in those with MS than in those without DM or MS although the differences for MS were not significant. In compare with Non-DM and Non-MS, patients with DM were 1.9 times more likely to have CAD ($p < 0.05$) and patients with MS were 1.3 times more likely to have CAD although the p value for MS is not significant.

CONCLUSIONS: In this population of Asian Chinese with suspected CAD, multi-vessel CAD was more common in patients with DM and those with MS. The most frequent components of MS in these patients were high blood pressure 75%, decrease HDL 96% and increase triglycerides 93%. It is definitely sure that Asian Chinese with DM are at high risk for CAD. We still need to do further study for MS and CAD relationship and larger number of patients may help for stronger correlation.

Abstract # 14

IF I WEAR A NECKTIE, DOES MY PRESSURE GO UP? C. Teng[1], R. Gurses-Ozden[2], J.M. Liebmann[2,3], C. Tello[2,3,4], R. Ritch[2,3] ,SUNY Downstate Medical Center, Brooklyn, NY 11203
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Purpose: To evaluate the effect of tight neckties on intraocular pressure (IOP) measurement using Goldmann applanation tonometry.

Methods: The same examiner measured IOP in both eyes of 20 normal subjects and 20 open-angle glaucoma patients. IOP readings were taken with an open shirt collar, 3 minutes following placing a tight necktie and 3 minutes after loosening it. The examiner was masked to the IOP reading and the IOP was recorded by an independent pressure reader. The measurements were compared by paired t-test.

Results: All subjects were male and wore collared shirts. Normal subjects were younger than the glaucoma patients (mean age, 35.1 ± 9.6 (range, 21 to 57 years) vs. 62.2 ± 11.4 years (range, 42 to 75 years), $p<0.0001$; respectively). Mean IOP in normals increased by 2.6 ± 3.5 mmHg ($p<0.0001$, paired t-Test; range -3 to 14 mmHg) and in glaucoma patients by 1.0 ± 1.6 mmHg ($p=0.0005$, paired t-Test; range -2 to 4.5 mmHg). In normal subjects, IOP of 24 eyes was increased by ≥2 mmHg and 15 eyes by ≥4 mmHg. In glaucoma patients, IOP of 13 eyes was increased by ≥2 mmHg and 3 eyes by ≥4 mmHg.

Conclusion: The presence of a tight necktie increases IOP both in normal subjects and glaucoma patients. In some patients the increase was more than 4 mmHg. This could predispose patients to glaucomatous neuropathy and could affect the clinical management and diagnosis of glaucoma.

Abstract # 15

MICROCOCCUS INFECTION IN PATIENTS RECEIVING EPOPROSTENOL BY CONTINUOUS INTRAVENOUS INFUSION Richard L. Yap, MD and Leonard A. Mermel, DO, ScM, Department of Medicine, Brown University School of Medicine and Rhode Island Hospital,593 Eddy Street, Providence, RI 02903

Epoprostenol has been associated with catheter-related infections. Our hospital noted several cases of *Micrococcus* bacteremia in patients with pulmonary hypertension receiving this drug. Our objectives are to show an association between *Micrococcus* bacteremia and patients receiving epoprostenol. A retrospective chart review of 15 patients receiving epoprostenol was done between January 1, 1997 and December 31, 2000. Six patients had 17 episodes of catheter-related infections. *Micrococcus* was isolated in 35% of all catheter-related infections and 60% of all cases of catheter-related bloodstream infections. All the patients had Hickman catheters placed at the subclavian vein by a single surgeon. In comparison with all the catheters placed by this surgeon in the same time period, there were 4 *Micrococcus* catheter-related bloodstream infection out of 30 catheters placed for the epoprostenol group while there was none out of 426 catheters placed on the control group ($p=0.00002$). In conclusion, there is a significant association between *Micrococcus* catheter-related bloodstream infection and patients receiving epoprostenol by continuous intravenous infusion.

Abstract # 16

Delayed Accelerated Hyperfractionated Radiation with Concurrent Cis-platinum Without Induction Chemotherapy for Organ Preservation Therapy of Stage III/IV Head and Neck Cancer.

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Two important treatment advances in locally advanced head and neck cancer have been the demonstration that delayed accelerated hyperfractionated radiation (DAHF) and the use of concurrent platinum-based chemotherapy independently improve outcome compared to conventional radiotherapy alone. The current challenge is to define a optimal chemoradiation regimen which is effective in controlling disease with acceptable morbidity and that may be amenable to the incorporation of effective biologic therapeutics. Based on our previous experience treating unresectable head and neck cancers patients, we initiated a phase II trial delivering cis-platinum (CDDP) concurrent with delayed accelerated hyperfractionated radiation for the purpose of organ preservation. The regimen was similar to the one studied in the recently completed RTOG 99-14 trial. No induction or adjuvant chemotherapy was given and only 2 cycles of cisplatinum were administered.

Thirty-three patients with AJCC Stage III/IV (76% IV, 4 unresectable) of the larynx (n=20), oropharynx (n=7), hypopharynx (n=5) and oral cavity (n=1) were treated with DAHF to 70Gy/6 weeks (BID RT last 2 weeks, 6 hour interfraction interval) with concurrent CDDP (100mg/m2) on weeks 1 and 4 of radiation. Patients with >N2 underwent planned neck dissection after receiving 60Gy to the involved nodes. Ninety-one percent (30/33) were able to complete the chemoradiation treatment, of whom 10 required treatment breaks of no more than 3 days. Three patients stopped treatment at 65Gy due to nadir sepsis (n=2) or confluent mucositis (n=1). Using RTOG criteria, grade ≥3 acute toxicities occurred in 24% (8/33) primarily mucositis (7 grade 3) and one septic death. Although 42% of patients were not anemic (Hgb < 12.5 females, < 13.5g/dl males) prior to treatment, all patients except one became anemic with a median hemoglobin drop of 2.3 g/dl (1.1-5.7g/dl). The median percentage weight loss was 9% (0-21%). Perioperative mortality occurred in one patient. Among the 30 patients evaluable for chronic toxicity evaluation at ≥3 months, 6 patients experience grade 3 or 4 chronic toxicity—4 with dysphagia to liquids and solids requiring prolonged PEG tube dependence and 2 patients developing laryngeal chondronecrosis, one requiring laryngectomy. Voice was good to excellent (RTOG Gr 0-1) in 87%. All patients except one developed chronic Gr1-2 xerostomia.

At a median followup of 14 mo (0-31 mo), the complete response rate at the primary site was 82% with persistent primary disease in 6 patients, all of whom have died—4 from progressive disease, one from perioperative complications following laryngectomy, and one from sepsis at the end of treatment. Three patients have died of distant metastases, 2 with locoregional control. The crude rates of locoregional control, disease-free survival and overall survival are 79%, 79% and 71%, respectively. The crude rate of organ preservation was 91% (30/33) for all patients.

Conclusion: The addition of concurrent CDDP to DAHF is tolerable in the majority of patients with high compliance rates. However, given the significant acute and chronic toxicities, multidisciplinary supportive care is necessary to minimize their severity. Complete response rates are excellent with high rates of locoregional control and organ/function preservation. This organ preserving approach should be considered for comparison with the concurrent chemoradiation arm established by RTOG 91-11 and the GORTEC trials using conventional fractionation radiotherapy and 3 cycles of CDDP.

Abstract # 17

Image Cytometric DNA analysis as a predictor of Barrett's Esophagus progressing to Esophageal Adenocarcinoma. Ming Fang[1], Michael Klein[2], Edward Lew[1], Yan Zhang[3], Rongzhen Chen[3], Ying-Hao Su[2], and Raj K. Goyal [2], Boston, MA 02115

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It has been reported that the finding of DNA content abnormalities such as aneuploidy and tetraploidy, in flow cytometric DNA analysis (FCDA) of fresh biopsy tissue from Barrett's Esophagus (BE) indicate a high risk for subsequent development of esophageal adenocarcinoma. We have shown that image cytometric DNA analysis (ICDA) of formalin-fixed, paraffin-embedded archival tissue can reliably detect aneuploidy and tetraploidy. Biopsy tissues from five patients with BE who were on endoscopic follow-up and subsequently developed esophageal adenocarcinoma were examined with ICDA. Two of the 5 patients progressed from BE with high grade dysplasia to adenocarcinoma, whereas three others progressed from BE with indefinite or low grade dysplasia to adenocarcinoma.

Case #1 had an initial biopsy showing BE only which had mixed diploid and aneuploid cells; five months later, follow-up biopsy revealed BE with LGD, again with mixed aneuploid and diploid cells; 6 years later, this patient developed esophageal adenocarcinoma which showed aneuploidy. Case #2 had an initial biopsy of BE/LGD with aneuploidy; 13 months later, the patient developed adenocarcinoma again with aneuploidy. Case #3 had an initial biopsy showing BE with high grade dysplsia (HGD) and aneuploidy; repeat biopsy one month later showed adenocarcinoma with aneuploidy. Case #4 had an initial biopsy showing BE/LGD with diploid cells, but with a high percentage of cells in S phase mixed with a tetraploid cell population; 8 months later, the patient developed adenocarcinoma with aneuploidy. Case #5 had an initial biopsy showing BE/HGD, which had diploid and aneupoid cell populations; follow-up biopsy 2 months later revealed adenocarcinoma with aneuploidy.

In conclusion, ICDA showed that all five patients who subsequently developed adenocarcinoma had DNA content abnormalities in earlier biopsies regardless of the grade of dysplasia. This retrospective study shows that examination of DNA abnormality using ICDA may helpful in identifying patients with BE who are at high risk for developing adenocarcinoma.

Abstract # 18

Temozolomide for Childhood Low-Grade Glial Tumors

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Background: The optimal treatment for unresectable or recurrent childhood low-grade gliomas (LGGs) is undefined. Temozolomide (TM), which has shown efficacy in high-grade gliomas, may have utility against LGGs.

Objective: To assess the efficacy and tolerability of TM in children with LGGs.

Design/Methods: Since 1999, 13 children from 6 months to 19 years of age with LGGs and MRI evidence of unresectable tumors have been treated with oral TM. Two patients were treated following diagnosis and incomplete primary resection or biopsy. Three patients without biopsies were treated at the time of tumor progression. Eight patients had prior therapies (surgery, radiotherapy and/or chemotherapy) with residual disease and were treated with TM at tumor recurrence. Pathological examination showed juvenile pilocytic astrocytomas in 6 patients, fibrillary astrocytomas in 2 patients, and a ganglioglioma in 1 patient. Four patients were not biopsied. Four patients received a 5 day regimen (TM 150-200mg/m^2/day x 5 days every 28 days) and 9 patients received a 42 day regimen (TM 75mg/m^2/day x 42 days every 56 days).

Results: A total of 46 cycles of the 5 day regimen and 55 cycles of the 42 day regimen have been given. Three patients demonstrated partial tumor response to TM, 2 of these on the 42 day regimen. One of these 3 continued to have tumor response for 14 months after TM discontinuation. The median time to maximal MRI response was 5 months (range 4 to 23 months). Four patients (all on the 42 day course) demonstrated tumor progression while on TM. The median time to progression was 12 months (range 1 - 12 months). Six other patients have had stable disease since starting TM. Among the 5 patients who had prior chemotherapy and/or radiation therapy, TM induced disease stabilization in 3 and tumor response in 1. In the 3 patients with neurofibromatosis-1, 2 patients had tumor responses and 1 had disease stabilization. Patients who progressed on TM were treated with other therapies and all the 13 patients are currently alive with no evidence of progressive disease.

Thrombocytopenia, nausea, emesis, and fatigue were the most common toxicities. Five patients (4 on the 5 day course) developed thrombocytopenia. Platelet transfusions were given to 4 patients, one of whom discontinued TM thereafter. Two patients developed neutropenia, one of whom developed febrile neutropenia twice. Two patients, one of whom was hospitalized briefly for abdominal pain, nausea, and dehydration, discontinued therapy because of fatigue, nausea and/or emesis. Three other patients also had nausea or emesis. Three patients experienced fatigue. One patient developed worsening of her preexisting reactive airway disease and discontinued TM after one year. One patient developed shingles.

Conclusions: Temozolomide is active and well-tolerated in children with LGGs. Moreover, TM is also effective in patients who had prior therapies. The 5 day course may be more active in preventing tumor progression, but the 42 day regimen is less toxic than the 5 day regimen. Any impact upon survival for these patients remains to be demonstrated.

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