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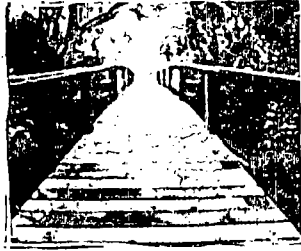
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The River Fund



July 14, 1999

SERVING PEOPLE IN NEED

Sandy Thurman
C/o Cheryl Gaurle
White House Office of National AIDS Policy
736 Jackson Place
Washington, DC 20503

Dear Sandy:

Thank you for meeting with us during the ANIN Council gathering. I am sending this packet to follow up with your discussion with Brahma Das regarding the White House meeting of spiritual leaders involved with AIDS, and also about the possibility of having a follow-up meeting at the Parliament in South Africa. He also discussed the appropriateness of Ma Jaya's participation, as she is a Trustee of the Parliament and will be attending in Cape Town.

So you can understand a little more about who we are and what we do, I am enclosing a proposal for the South Africa Project. At the Parliament of the World's Religions, The River Fund will provide urgently needed HIV educational outreach, and will share our collective vision of selfless service and caregiving for people with AIDS. The Parliament venue offers a unique opportunity to pilot test this initiative with perhaps the most diverse convocation of religious leaders in the world.

We will be taking an American national treasure, the AIDS Memorial Quilt, to the Parliament for the first time, and to the **Global AIDS Interfaith Network (GAIN)**, created as part of this initiative. As planning members of GAIN, we are developing an HIV/AIDS curriculum providing five AIDS and ministry workshops during the Parliament conference; and a one-day institute offsite which will be open to local and regional AIDS ministers and community leaders who cannot attend the Parliament.

I am also enclosing a **Statement of Conscience from People of Faith about the AIDS Pandemic** which I urge you to sign and return. After gathering as many signatures as possible, the Statement will be presented at the Parliament Multi-Faith Prayer Vigil and Quilt Display on World AIDS Day, and Parliament delegates will also be encouraged to sign throughout the conference.

³⁸⁸⁻⁰⁹⁹
Brahma Das is out of town with the Dalai Lama until the end of this week. The River Fund phone number is 561-589-5076 if you have any questions. Thank you for all your efforts on behalf of those struggling with AIDS. We look forward to talking with you soon.

Warm regards,

Kumari Mullin
Program Director

1155 Roseland Road, Unit Sixteen, Sebastian, FL 32958

tel: (561) 589-5076 • fax: (561) 589-5052

web: www.riverfund.org • e-mail: riverfund@aol.com



Kashi



On the way to God,
stop and touch humanity.



Every human being deserves
to be heard, to be loved,
to be touched.



Am I black or white,
I have never decided.
Nor do I need to.



AN OPEN APPEAL TO PEOPLE OF FAITH ABOUT THE AIDS PANDEMIC

I am writing to ask the world's spiritual leaders and all people of faith to come together and reach out in caring for those suffering from the AIDS pandemic.

The attached Statement of Conscience will touch millions if we let it flow from all of our hearts, following our own faiths and traditions. This Statement is not just about spiritual leaders. It is about the child in front of us, or often the shadow of what that child used to be.

There are whole generations of young men, women and children dying from a disease that no one seems to be able to find a cure for. We are asking all religious leaders and people of faith to join us in reaching out to the people hardest hit by this AIDS pandemic.

December 1st is designated internationally as World AIDS Day. This year at the gathering of the Parliament of the World's Religions in Cape Town, South Africa, the River Fund will host a display of the AIDS Memorial Quilt and a multi-faith prayer vigil at which this Statement of Conscience will be presented.

Eight million children have already been orphaned by AIDS in sub-Saharan Africa. We all need to be the mothers and fathers of these children by opening up our temples, churches, gurdwaras and mosques. And we need to open our hearts along with our places of worship.

We are gathering the names of people of conscience. We're asking you to put your name to this statement, for if we don't support such a document, who are we?

We have many urgent concerns, which we share in the attached Statement of Conscience. I urge you to join us in supporting this proclamation. On behalf of all people who are suffering, thank you.

Namaste (the light in me bows to the light in you),

MA JAYA BHAGAVATI

Trustee of the Parliament of World Religions, Founder of Kashi Ashram and of the River Fund, serving people with AIDS and other life challenging illnesses

P.S. Please sign the enclosed Statement and return to THE RIVER FUND at 11155 Roseland Road, Unit 16, Sebastian, FL 32958 USA or fax to (561) 589-5052. If you have any questions or comments, please call (561) 589-5076.



STATEMENT OF CONSCIENCE FROM PEOPLE OF FAITH REGARDING THE HIV/AIDS PANDEMIC

Whereas, The Parliament of World Religions, a gathering of religious and spiritual leaders from throughout the world, will convene in Cape Town, South Africa on December 1, 1999,

And whereas, December 1st is designated by the World Health Organization and the United Nations as World AIDS Day,

And whereas, South Africa is among those nations struck hardest by the pandemic, with an estimated 20% of the total population infected with HIV,

And whereas, Over eight million children have already been orphaned by AIDS in sub-Saharan Africa,

And whereas, New treatments for HIV, which have dramatically reduced the death rate from AIDS within the developed nations of Europe, North America and Australia, are unavailable to the vast majority of people living with AIDS in African and other developing nations,

And whereas, People living with AIDS everywhere face persecution, discrimination, social rejection and often violence against themselves and their families,

Now, be it resolved, that the undersigned people of faith, representing many faith traditions in the world's religious community, affirm:

- 1) All people living with AIDS are children of God, fully deserving of love, compassion, care and human dignity.
- 2) The wealthy nations must share their resources with those parts of the world where the need is greatest, and the full resources of those nations must be directed towards the search for effective treatment and a vaccine.
- 3) All nations must accelerate their efforts to reduce HIV transmission – by using public education, particularly HIV prevention campaigns for the world's youth.
- 4) That the persecution of people with AIDS must end.
- 5) And further, we call upon the world religious community and individual people of faith everywhere, to observe December 1, 1999 with vigils, prayers, fasting and service as a World Day of Prayer for Africa and for the global struggle against AIDS.

This Statement was drafted by MA JAYA BHAGAVATI (Trustee of the Parliament of World Religions, Founder of Kashi Ashram and of the River Fund, serving people with AIDS and other life challenging illnesses) and CLEVE JONES (Founder of the AIDS Memorial Quilt and the NAMES Project), and is enthusiastically endorsed by a host of spiritual leaders, faith practitioners and human rights activists.

Please sign below and return by mail to the River Fund, 11155 Roseland Road, Unit 16, Sebastian, FL 32958, USA or fax to (561) 589-5052. If you have any questions or comments, please call (561) 589-5076.

Signature

Print Name and Title

Kashi Church Foundation South Africa Project

This December at the Parliament of the World's Religions Conference in South Africa, the **Kashi Church Foundation** is being honored as one of the "Guiding Institutions". We are being asked to share our multifaceted approaches to care-giving, education, and spiritual enrichment. As a spiritual leader and Trustee of the Parliament, Ma Jaya Sati Bhagavati, founder of the **Kashi Church Foundation**, was invited to present her teachings on spirituality and service. The Parliament was originally founded in 1893 to establish a dialogue between the spiritual traditions of the East and the West. In 1993, it was reborn in Chicago, where 7000 people from all over the world came together to celebrate diversity and harmony and to explore religious and spiritual responses to the critical issues facing today's world. This year, at least 8000 delegates and over 350 spiritual leaders from around the world are expected to attend the Parliament.

This year, the Council for a Parliament of the World's Religions will present a new document, A Call to our Guiding Institutions. The Call is addressed to society's guiding institutions of government, business, education, media, and religion asking each to reflect on its proper roles at the threshold of the next century and the next millennium.

- ▼ The **Kashi Church Foundation** based on Ma Jaya's teachings of kindness and service, was established in 1976. Kashi Ashram is a residential spiritual community that embraces the sacred practices of many traditions. The essence of the teaching is based upon a commitment to humanity through service. Those at Kashi are dedicated to providing an environment that fosters spiritual renewal for both the young and old. Ma Jaya and all at Kashi are advocates of human rights and equality and known for their compassionate work with death and dying and caring for those in need. It is through this commitment to humanity by Ma Jaya and Kashi that both the **River Fund** and **River School** were born.
- ▼ **The River Fund**, directed by Kashi resident, Bina Frank, is a not-for-profit organization dedicated to taking care of the people with life challenging illnesses. **The River Fund** is also the Central Florida Chapter of Names Project AIDS Memorial Quilt and is responsible for AIDS education programs and quilt displays in Florida. Because of Kashi's involvement in the Parliament, one of the largest displays of the AIDS Quilt will take place in South Africa.
- ▼ Another important aspect of the Kashi Church Foundation is education. Ma Jaya and Dr. Thomas B. Byrom, former Harvard and Oxford professor, co-founded **The River School** in 1979. The school was established to create a safe learning environment free from the bigotry and prejudice which is prevalent in today's public schools. **The River School** provides its students, from the ashram and surrounding communities, with an environment that weaves spirituality, service, and awareness into a quality education.

In addition to establishing the **Kashi Church Foundation**, Ma Jaya founded World Tibet Day –an annual event in early July that supports the Tibetan peoples' right to religious, cultural, and political freedom. Last year, on the Dalai Lama's birthday, there was a national observance of World Tibet Day. This year World Tibet Day will be celebrated in over 50 cities as well as interfaith services in over a thousand houses of worship around the world.

The South Africa Project will provide **Kashi Church Foundation** with a global forum within which to continue our service to humanity and create an impact that will be felt worldwide during the 21st century.

Enclosed there are descriptions of projects that **Kashi Ashram**, **The River Fund**, and **The River School**, will be presenting and initiating as part of our answer to The Call of the Parliament. Also enclosed is the joint budget for the South Africa Project.



Kashi

South Africa Project. Kashi Ashram

Our Hands Reach Out To Love, Teach and Serve

Ma Jaya was first invited to the Parliament in 1993. As a spiritual leader committed to service, she played a major role in drafting the ground breaking document, Towards a Global Ethic: An Initial Declaration, which set forth the ethical common ground shared by the world's religious and spiritual traditions. Ma Jaya emphasized the importance of including the following issues in the Global Ethic document:

- ▼ a commitment to a culture of equal rights for all humanity
- ▼ a commitment to continuing the global fight against AIDS
- ▼ a commitment to a culture of spiritual and religious freedom

This year, Ma Jaya and other representatives of Kashi have the opportunity to respond to "The Call" of the Parliament. The following are Kashi Ashram's projects and workshops, which will contribute to this global effort.

Kashi Ashram Millennial Workshops/Projects:

▼ Ma Jaya: the Rise of Spirituality in the 21st century:

Ma Jaya Sati Bhagavati will offer her teachings and insights into the merging of the feminine and the masculine and how this can initiate a change into the 21st century. Ma Jaya's expression of God and spirituality asks for all to live in the moment, be of service, and wake up to "The Call".

▼ Global Awareness Campaign:

Kashi Foundation will sponsor a campaign using not only 21st century media, but also education at a grassroots level to raise awareness against any racism, bigotry, and prejudice. This campaign will be in the form of public service announcements, online broadcasting, web sites, proactive documents and global dialogue. The first phase of the campaign, already in production, is the "Statement of Conscience from People of Faith Regarding the HIV Pandemic and Individuals Living with AIDS". This is a document, initiated by Ma Jaya, which will be signed by key religious leaders and thousands of others stating that people living with AIDS are fully deserving of love, compassion, care, and human dignity.

▼ Kashi Retreat and Conference Center for Advanced Spiritual Studies:

For the last 22 years, the Kashi Foundation has offered educational, spiritual, and holistic retreats, conferences, and workshops to seekers of all faiths. The Kashi Center will provide a forum for those seeking interfaith dialogue and spiritual renewal. Kashi is now expanding through the development of the Kashi Center for Advanced Spiritual Studies, a multi-dimensional study and retreat center dedicated to the spiritual advancement of humanity.

▼ Kashi – Life in Community:

During the Parliament, a team of young adults from Kashi and other communities will discuss the different aspects of growing up in spiritual communities. Kashi is also creating a book and has produced a video that depicts the positive attributes of children that have grown up in community. How they foresee their place within the 21st century will illustrate the impact that this has upon their lives.

About Kashi Ashram

Kashi embraces diversity, bridges cultures and values, and contributes global perspectives for the future. All of the Kashi ashrams, in Florida, New York, Los Angeles, and Atlanta, are dedicated to enriching the lives of individuals who are seeking to deepen their awareness, stimulating their intellect, and challenging themselves to transform their lives and renew their spiritual path. Kashi provides an environment that initiates interfaith dialogue and religious freedom, and fosters world peace.

Each project will be a continuing effort into the future and complements The Parliament of the World's Religions' Call to the Guiding Institutions.



South Africa Project: The River Fund

"There are no throw away people... Every human being deserves a chance to be heard, to be loved, to be touched." Ma Jaya, founder

The River Fund will present a workshop entitled "Spirituality and Service in the 21st Century: A Model of Caring", focusing on the essence of service and how The River Fund has answered our communities' call to action. We will display the AIDS memorial quilt for the first time at the Parliament. We are on the planning committee for a one-day regional AIDS institute, called the Global AIDS Interfaith Network (GAIN) for South Africans who are unable attend the Parliament. Our goal is to inspire spiritual and community leaders from around the world to answer the call to service in their countries, and to engage in a global dialogue about the AIDS pandemic.

River Fund Millennial Projects

▼ 40-bed Care and Wellness Center

A state-of-the-art assisted living facility for 40 residents, complete with a holistic wellness center.

▼ "An Evolving Vision of Service" Photo Documentary

"To slumber on this Earth when there is such a need to serve is truly a sad thing," Ma Jaya writes. In honor of the millennium and our 10th anniversary, the River Fund will create a photo essay documenting the incredible transformations we have all experienced through service.

▼ Statement of Conscience to End Persecution of People with AIDS

River Fund founder Ma Jaya has initiated a Statement of Conscience to call upon the world's faith leaders to speak out against the persecution of people with AIDS, culminating with a prayer vigil and press conference at the Parliament Quilt display on World AIDS Day.

About the River Fund

Founded by Ma Jaya in 1990, The River Fund is a non-profit organization dedicated to serving people who are alone and in need, especially those with HIV/AIDS and other life challenging illnesses. The River Fund receives no government funding and relies solely on private donations.

River Fund Programs:

- ▼ The River House - a unique residence providing a healing environment, home cooked meals, counseling, and a variety of holistic programs. Residents are invited to participate in Kashi, an interfaith spiritual community offering yoga and meditation on a beautiful 86 acre retreat site. The River House serves people who have no other options.
- ▼ Mary's House - a residence for abused and terminally ill babies, especially those with AIDS.
- ▼ Visitation Program - volunteers and River House residents regularly visit hundreds of hospitals and nursing homes in Florida.
- ▼ AIDS Prevention and Education - last year our AIDS educators taught in 80 schools reaching 25,000 students, and 25 churches of all denominations.
- ▼ Central Florida Chapter of the NAMES Project AIDS Memorial Quilt - The River Fund is the largest Quilt chapter in Florida.

Related Projects:

- ▼ River Fund New York - provides food and clothing to the hungry and homeless in the New York City area through *The Moveable Feast* and *Street Relief* programs. Volunteers visit hundreds of individuals in care facilities on a weekly basis.
- ▼ Kashi Los Angeles - The *G.I.V.E.* program directs volunteers to service organizations and care facilities within Southern California. *Under the Bridges and on the Streets* distributes full meals and clothing directly to homeless people on the streets in Los Angeles.

In the United States, Florida ranks number one for heterosexual AIDS cases, number two for pediatric AIDS and number three for overall AIDS cases. Researchers estimate that over 14% of South Africa's 32 million people are infected with HIV. Over 21 million people in sub-Saharan Africa are expected to die from AIDS in the next ten years; 8 million children are orphaned and at least one-third of these children are themselves infected with HIV.

South Africa Project: The River School

Education for the Heart, Mind and Spirit

In response to "The Call" by the Parliament of World's Religions, the River School will accompany Ma Jaya to South Africa. A group of staff and high school students will represent our vision of education, a model of how embracing diversity can offer students a broader, more global perspective.

The River School Millennial Workshops/ Projects:

▼ "The River School: A Model for Education in the 21st Century"

A workshop in which students and staff will discuss how their model of education can impact education in the next century.

▼ "Where Children of the Heart Dwell"

A play based on the Names Project AIDS Memorial Quilt in which the quilt "stories" come to life through drama, dance and music.

Inspired by our invitation to the Parliament, we have developed a permanent study program called the Global Awareness Project. The first phase of this program, which started in the winter semester 98/99, has been the study of South Africa's traditions, history and current events. As an enhancement to this global study program, the trip to South Africa will also include:

- ▼ Visits to South African service organizations, schools, and care centers, mainly in Cape Town.
- ▼ Visits to South African townships.
- ▼ Meetings with the pen pals the students have been writing to for the past year
- ▼ Tours of South Africa which will include a trip to the jail that held Nelson Mandela, a trip to Cape Hope, a hike on Table Mountain, visits to art galleries and museums, and will conclude with a safari game drive in Botswana.

About The River School

The River School was founded in 1979 by Ma Jaya and Dr. Thomas B. Byrom, professor at Oxford and Harvard Universities. The school serves the local community as a non-profit, college-preparatory school, preschool through grade 12. Our goal is to weave spirituality, service, and awareness into our dedication to providing a quality education. All of our graduates have gone on to college, most graduating with honors. Following Ma Jaya's example, the River School highlights its curriculum with the following service programs:

- ▼ Preschoolers through 4th graders sing for monthly programs at local nursing homes and care centers.
- ▼ Students in grades 5 through 12 volunteer during school hours at Mary's House, a respite for HIV-positive babies.
- ▼ Students visit patients at The River House, a residence for the terminally ill, and the West Palm Beach County Home.
- ▼ The high school's AIDS and Issues Team uses the arts to present AIDS peer education programs in area schools and health centers.
- ▼ Participation in state and national events for the Names Project AIDS Memorial Quilt.
- ▼ In cooperation with The River Fund, the school is initiating a pilot project which will provide family-type homes and education for children of parents who are terminally ill, or who have died from AIDS and other diseases.

When they return, our students will share their experiences with area schools by presenting the workshop and play, along with a video and photographic presentation of their trip.



Kashi

Overall Budget
Parliament of World's Religions in South Africa
26 Nov. '99 - 13 Dec. '99

Kashi Ashram Budget

Administrative Personnel

Personnel \$50,150

Marketing

Communications \$3,000
Office supplies \$1,625
\$4,625

Travel Expenses

Airfare \$12,168
Accommodations \$11,178
Per diem \$11,340
Parliament Registration \$1,800
Meeting Room \$2,600
Communications \$1,000
Baggage charges \$1,500
Transportation Rental \$3,000
Tips/Misc. \$1,260
Advance Staff \$2,500
Video \$10,000
\$58,346

Kashi Ashram Total = \$113,121

River Fund Budget

Administrative Personnel

Personnel \$29,833

Marketing

Communications \$2,660
Office supplies \$1,500
\$4,160

Travel Expenses

Airfare \$10,816
Accommodations \$9,936
Per diem \$10,080
Parliament Registration \$2,000
Quilt transport \$3,500
Communications \$800
Baggage charges \$1,160
Transportation Rental \$3,000
Tips/Misc. \$1,440
Advance Staff \$2,100
Photo Documentary \$10,000
\$54,832

River Fund Total = \$88,825

River School Budget

Administrative Personnel

Personnel \$41,833

Marketing

Communications \$1,850
Office supplies \$1,500
\$3,350

Travel Expenses

Airfare \$36,504
Accommodations \$14,580
Per diem \$34,020
Parliament Registration \$5,400
Safari Adventure \$17,500
Communications \$1,500
Baggage charges \$580
Transportation Rental \$1,500
Tips/Misc. \$4,860
Advance Staff \$1,500
Video \$10,500
\$128,444

River School Total = \$173,627

Project Total = **\$375,573**
Kashi In-Kind Donation = \$91,362
Contributed Donations = **\$64,000**
Total Funding Needed = \$220,211

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H. R. Shepherd

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AT GEORGETOWN UNIVERSITY

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VIA FEDERAL EXPRESS

June 3, 1998

Ms. Sandra Thurman
Director
Office of National AIDS Policy
736 Jackson Place NW
Washington, DC 20503

Dear Sandra:

I am sending you this important document which is the thesis of Erica Seiguer. I am sure you met and discussed the AIDS pandemic with her. I think you will find this thesis very helpful. If I had a magic wand, I would urge you to share this document with the President who is trying so hard to make things happen.

Would very much like to talk to you about these recommendations and get your views on them.

Additional copies are being printed, and if you would like others to have this document, I will be glad to see that they get a copy.

Sincerely,



H. R. Shepherd
Chairman



HRS:kb
Enclosure



GEORGETOWN UNIVERSITY

58 Pine Street New Canaan CT 06840
203-972-7907 facsimile 203-966-4763

Building D Suite 154 4000 Reservoir Road NW Washington DC 20007
202-687-9145 facsimile 202-687-9242 e-mail shepherdh@sabin.georgetown.edu

Dedicated to Disease Prevention

November 27, 2000

Sandra Thurman,
Director White House Office of National AIDS Policy
The White House
Washington DC 20500

Dear Ms. Thurman,

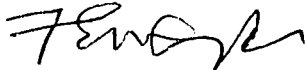
You may want to know about a Patent recently approved for a new Viral treatment formulation for HIV/AIDS, dengue fever and influenza. The United States Patent and Trademark Office (PTO) approved the patent in August, 2000. The formulation has the advantages of being very effective against the symptoms of HIV/AIDS, easier to test, "cheap" to produce (composing of US-FDA approved generic drugs,) and easier for patients to use as compared to current cocktail drugs.

We are offering the patents for outright purchase, although other collaborative arrangements for clinical investigation are possible. We are aware of your commitment to addressing the epidemic of HIV/AIDS especially in Africa. We would like you to recommend us to a biotechnology or a pharmaceutical company which has the commitment, know-how and funds to introduce the formulation to the market in developing and developed countries. Alternatively, you could assist in providing us with funds so that we could conduct the clinical trials with the collaboration of physicians, community members, and patients especially those living in rural areas.

Details of the patented new products are enclosed. Please contact us at the address below for further information because we are eagerly waiting to hear from you.

Thank you

Sincerely,



Dr. Eke F. Wokocha.
7439 Broadway
Lemon Grove, CA91945
(619) 300-1747.

cc- Ruben G. Fabunan, M.D.
Enclosures

Executive Summary

New Viral Treatment Claimed for Influenza, Dengue and HIV/AIDS

A medical doctor has developed a formulation consisting of US-FDA approved generic drugs (U.S.P.), which have been demonstrated to be effective in the treatment of dengue fever and influenza. Curative results have been obtained repeatedly for these two viral conditions. The formulation has recently been used to help mitigate symptoms associated with HIV/AIDS. Upon treatment with the formulation, the patient exhibited a dramatic increase in CD4 counts and a marked improvement in mental and physical well-being. The AIDS patient continues to undergo periodic treatment with the formulation and has resumed normal daily activities as a consequence of the treatments.

Besides its apparent efficacy in treating serious and even life-threatening conditions, the formulation has the added advantage of being very accessible and "cheap". This feature would make it particularly attractive for use in under-developed and developing countries where dengue fever and AIDS are epidemic but where many Western drugs are simply unavailable due to their prohibitive cost.

Currently, no specific treatments for dengue fever are available. Expensive treatments for HIV/AIDS are available in industrialized countries but recent statistical data indicate that the effectiveness of AIDS drugs is dropping due to a buildup of drug resistance by the HIV virus. In addition, the AIDS drugs lead to serious side effects in a significant number of patients. The cost effective injectable formulation may represent a very attractive addition to the AIDS drug arsenal and provide a simple yet effective way of treating serious, potentially life-threatening illnesses such as dengue hemorrhagic fever.

Presently, a U.S. Patent was issued which covers Snakebite Antidote and other animal poisons; First Place award in Biotechnology at the Invention Convention held in Pasadena, California on August 31, 1997. Another patent on the formulation was filed in September 1999, which covers the viral treatment applications for Influenza, Dengue, and HIV/AIDS. Status: US Patent approved – August 2000.

The independent inventor seeks - **AN OUTRIGHT SALE** - with a biotechnology or pharmaceutical company, which has the commitment and know-how to introduce useful and cost effective treatments to under-developed, developing, and industrialized countries. The two key elements to successful commercialization will be 1) the procurement of statistically significant data in clinical trials designed for proving the efficacy of the formulation in treating given viral or animal poison conditions; and 2) overcoming distribution-related difficulties in under-developed and developing countries by working closely with local governments and possibly philanthropic organizations such as WHO.

A manual, which describes the clinical results, which have been obtained with the formulation at the Fabunan clinic in the Philippines to date or a video clip of the HIV/AIDS patient for demonstration, is available upon the signing of a Confidentiality Agreement.

EFW Global Enterprises

Advertising and Marketing Company

Dr. Eke F. Wokocho
President

7439 Broadway
Lemon Grove, CA 91945

Tel: (619) 300-1747
Fax: (619) 463-5438
e-mail: nosike@aol.com

Executive Summary

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President

7439 Broadway
Lemon Grove, CA 91945

Tel: (619) 300-1747
Fax: (619) 463-5438
e-mail: nosike@aol.com

HIV/AIDS
(Chimpavir-Fabunan Injection)

The Use of the Fabunan Viral Treatment (Chimpavir-Fabunan Injection) in the Treatment of HIV/AIDS

I Physiology and Epidemiology

Acquired immunodeficiency syndrome (AIDS) is caused by the retrovirus, human immunodeficiency virus (HIV). It was co-discovered by Dr. Robert Gallo and Dr. Luc Montagnier (see news clipping - Time Magazine, March 29, 1999). It is transmitted mainly through 1) sexual contact, 2) infected blood (e.g., by transfusion or by needle sharing) and 3) perinatal transmission from mother to infant. AIDS is a global disease which affects wealthy, industrialized nations as well as poor, developing/third world countries. The AIDS crisis in wealthier countries has been eased due to the availability of expensive drug treatments. However, the number of new cases (news clipping - Los Angeles Times, November 24, 1999) and the death toll continues to grow in poor countries partly because of the unavailability of "cheap" drug treatments. Africa, Asia and Latin America have the highest rates of new infections.

The HIV virus indirectly causes death by infecting and killing the T4 lymphocytes known as helper T (CD4) cells. HIV positive individuals who exhibit CD4 levels of less than 400 cells per mm³ of blood have a high probability of developing opportunistic infections namely pneumocystis pneumonia, Kaposi's sarcoma, shingles, toxoplasmosis, and tuberculosis. The HIV virus can also infect brain monocytes and macrophages thereby leading to symptoms of dementia of the central nervous system.

Individuals who are infected with HIV will generally have the infection for life. However, the progression of the infection may vary from individual to individual with respect to the timing of the onset of the disease's three stages. These three stages are cited below:

Stage	Clinical Manifestations
The early acute stage	• Begins 2 - 4 weeks after infection • Antibodies appear from 2 - 6 months after infection • Mononucleosis like symptoms • Number of CD4 cells usually normal (CD4 = 700-1000 cells per mm³ of blood)
The middle latent stage	• May last for years • Patient is asymptomatic • Virus is reproducing but remains confined to lymph nodes
The late immunodeficiency stage	• Decrease in the number of CD4 cells • Increase in the frequency and severity of opportunistic infection

II Current Treatment

"Our worst fears have become a tragic reality. AIDS drugs do not work for everyone and aren't a cure for anyone."

Steven Fisher, AIDS Action Advocacy Group

U.S. Federal research budget is about \$1.5 billion (news clipping - Los Angeles Times, August 18, 1999) excluding the drug companies where millions of dollars are being spent on an annual basis to develop effective drug treatments and/or a vaccine for HIV/AIDS. The three types of drugs currently available can be categorized as follows:

1. Nucleoside inhibitors of reverse transcriptase
 - a. Azidothymidine; *sold under the names AZT, Zidovudine, and Retrovir*
 - b. Dideoxyinosine; *sold under the names ddl, Videx*
 - c. Dideoxycytidine; *sold under the names ddc-Hivid*
2. Non-nucleoside inhibitors of reverse transcriptase
 - a. Nevirapine; *sold under the names Viramune*
3. Protease inhibitors
 - a. Saquinavir (sold under the name Invirase)
 - b. Ritonavir (sold under the name Norvir)
 - c. Indinavir (sold under the name Crixivan)

The purpose of all of the above drugs is to prevent replication of viral particles by CD4 host cells and therefore prevent the destruction of CD4 cells and the onset of life-threatening opportunistic infections. Category one and two drugs do so by inhibiting the action of reverse transcriptase, an enzyme which "prepares" the virus RNA or subsequent integration into the host cell's DNA. Category 3 drugs do so by preventing the protease-induced conversion of certain precursor proteins synthesized by the host cell from the integrated viral genetic material into the active proteins required for formation of the active viral particles.

Currently, the most effective treatment for HIV is a three-drug combination made of capsules and caplets form consisting of two nucleoside inhibitors and one protease inhibitor. The medical rationale for this treatment is based on the fact that viruses, including the HIV virus, have the ability to build up resistance to drugs through mutation. The triple drug combination is effective in inhibiting viral replication and also increasing CD4 cell counts.

The side effect associated with the current drugs range from merely bothersome to serious. For AZT, a former anti cancer drug in 1980's has the most common side effects like headache, nausea, vomiting, dizziness, a general feeling of poor health, and low red blood cell counts. Protease inhibitors are particularly problematic because they tend to interact with other kinds of drug to produce very serious side effects such as hematologic and hepatic toxicity and lipodystrophy (abnormal fat distribution in the body like abdomen, neck and thigh).

Although the above triple drug therapy have dramatically reduced the deaths from AIDS in developed countries, their high cost has made them a rarity in poor, underdeveloped and developing countries. In addition, the drugs appear to be losing their efficacy in developed countries. According to the Centers for Disease Control (CDC), the triple drug cocktail had caused a forty two percent decrease in AIDS deaths from 1996 to 1997. In August 1999 it was reported that the decline in deaths slowed to twenty percent from 1997 to 1998.

The CDC blamed the slowdown on three factors:

1. Some people are still not getting tested or treated for HIV virus.
2. The complicated regiment of pills makes it a difficult treatment program.
3. Drug-resistant strains of the virus are emerging.

The recent statistics strongly suggest that the drugs aren't as effective as had originally been hoped. However, it must be emphasized, that the observed decline in the death rate from AIDS is also due to social issues. Poor/low middle class people in the U.S. and other industrialized nations may not have access to the expensive AIDS treatment options that are available for insured, middle class individuals. For example, blacks who make up thirteen (13) percent of the population accounted for forty nine (49) percent of the deaths in 1998. The individuals who can afford to get treatment will probably continue to get treatment while those who cannot afford or have no insurance will not. Thus, the observed plateau in the decline of AIDS deaths should not be surprising given the social factors associated with the disease and the fact that the buildup of drug resistance by infectious disease agents such as the HIV virus is a fairly common occurrence.

The social issue described above is dramatically magnified in underdeveloped countries, particularly in Africa. In the United States, the three-drug cocktail for treating Aids cost about \$900 per month. This does not include other medical costs that might be associated with treatment (e.g., additional drugs, laboratory testing and/or hospitalization) of the opportunistic diseases caused by the virus. In a country such as South Africa where the average per capita income is \$6000, the AIDS drug cocktail is simply cost prohibitive.

At this time a reasonably priced, effective treatment for HIV/AIDS is not available. Even researchers who are trying to develop an HIV vaccine have admitted that the ability of the virus to mutate quickly may limit the efficacy of any new vaccine. Immune-based therapy which is intended to help individuals already infected with HIV to mount a strong immune response to the virus are receiving attention. Two such therapies undergoing evaluation are Interleukin-2 (IL-2; Proleukin[®]) and HIV-1 Immunogen (Remune[®]). Some encouraging results have been obtained with IL- when used in combination with current anti-HIV therapy, but the verdict is still out on HIV-1. However, IL-2 would also be an expensive therapy because it is a recombinant protein and therefore quite costly to manufacture.

III The Chimpavir-Fabunan Injection (CFI) in the treatment of HIV/AIDS

Dr. Ruben G. Fabunan has been working to improve the health of sick and infected patients in his former native Philippines for the past twenty four years. His Viral Treatment (Denguevir-

Fabunan Injection) has been shown to be highly effective in the treatment of dengue fever virus, including the particularly serious form of the disease, dengue hemorrhagic fever that HIV/AIDS follows the Dengue fever treatment model.

The Philippines is one of the developing country in Southeast Asia with HIV reported cases mostly overseas workers or persons infected by overseas workers or foreigners. In early 1999 about 1,300 HIV/AIDS cases were reported. Although there are more unknown number of individuals infected with AIDS, because of the strong social stigmatism associated with the disease in this strong Catholic country, individuals who know they have the disease tend to keep it to themselves, and many individuals who are infected with the disease probably do not know it.

Most Filipinos (Philippines) who are infected with HIV do not have the financial resources to pay the expensive drug treatments. The Philippines and African countries thus have something in common.

Individuals infected with HIV/AIDS who are not receiving treatment due to the high cost associated with currently available treatments.

In addition, a high percentage of the population in Thailand and Sub-Saharan Africa have HIV/AIDS. The current AIDS drugs regimens need to be carefully monitored by a healthcare professional, and individuals living in rural areas often do not have ready access to a health care facility.

Dr. Fabunan hypothesized that his Viral Treatment "Chimpavir-F Injection" may help improve the quality of life of HIV-infected individuals who have no access to other treatments by mitigating at least certain symptoms associated with AIDS. It is conceivable that such alternative or adjunctive treatment may also indirectly prolong the life of an HIV-infected individual because a mitigation of associated symptoms may help the infected individual "fight off" life threatening opportunistic infection.

As a compassionate treatment after an informed consent the clinical results obtained to date for an HIV-infected individual, E.S.B. has been treated with Dr. Fabunan's Viral Treatment, (CFI). It must be emphasized that these results are very preliminary, and that extensive clinical trials would need to be conducted to verify the efficacy of the treatment. However, the results strongly suggest that the treatment could have a beneficial effect on the health of at least some HIV-infected patients. It is also conceivable that even more pronounced benefits could be obtained if the Viral Treatment CFI were used in conjunction with the HIV drugs currently available. Perhaps most importantly of all, the Viral Treatment CFI is cheap and accessible thereby making a very attractive candidate for treating AIDS individuals in poor countries.

Three series of injections were given to the patient E.S.B., 47 year old, from May through July 1999. The number of injection days decreased from nine days in May to three days in July. It is Dr. Fabunan's belief that the treatment would consist of two parts.

1. an initial aggressive treatment in which two injections per day are given over the course of several days.
2. a maintenance regimen in which two injections per day are given on about two days per month.

The patient is now being treated according to the maintenance regimen and her CD4 counts are being monitored accordingly. Of course, the dosage treatment could be modified for other patients depending upon the CD4 count and the patient's response to the treatment.

The observation that the treatment results in an increase in CD4 counts is of particular interest because similar results have been obtained with other HIV drugs. An increase in CD4 counts is considered a benefit because the HIV virus destroys the immune system by attacking CD4 cells. The HIV cocktail drugs also reduces the viral load in the patient's blood because they interfere with the viral replication process. At this time it is not known whether the Fabunan Viral Treatment (Chimpavir-F Injection) has an impact on the viral load; this would be addressed in a formal clinical trial.

Another important results of the clinical study is that the patient's overall health status seemed to improve from both a mental and physical perspective. A healthier person will be more able to "fight off" opportunistic infections. In addition, the quality of a person's life is very much dependent upon his or her health. Even though it is highly unlikely that the Fabunan Viral Treatment (Chimpavir-F Injection TM) will treat a person of HIV, this very preliminary evidence suggests that it could help HIV infected individuals live happier and a more productive lives. This January 2000 (9th months), patient has been followed up closely and she has no pertinent complaints nor side effects.

In spite of the encouraging results obtained with the Fabunan Viral Treatment (Chimpavir-F Injection TM) much work still needs to be done to further evaluate its efficacy as a possible addition to the HIV treatment drug menu. Some possible areas for investigation during a formal clinical study are the following:

1. Will the Fabunan Viral Treatment (CF-I) allow the usage of lower cocktail dosages?
2. Will the CF-I, when used in conjunction with other AIDS therapies, yield additional benefits to the patient which are not present in the absence of the treatment?
3. Will the maintenance injections continue to maintain CD4 level? Could the current maintenance schedule be reduced further?
4. What, if any are potential long term side effects of the CF-I when used alone or in combination with other AIDS therapies?

The ready availability and cheap cost of the CF-I makes it a potentially attractive addition to the AIDS therapy market if its efficacy can be established during a formal clinical study. A downside of the CF-I is that it is an injectable treatment and therefore requires the "help" of healthcare professional. However, this mode of delivery has the advantage that lower dosages

are generally needed. It would seem that poor countries such as South Africa which are looking for cheap and effective treatments would improve their health infrastructure by setting up clinics in rural areas so that HIV-infected individuals could be treated by healthcare professionals. The World Health Organization may lend its support to such a program.

Also it is conceivable that the CF-I could be used in oral form or as a combination of oral and injectable therapies, depending upon the staging of the treatment.

FABUNAN MEDICAL CLINIC
Burgos, San Marcelino, Zambales C-2207 Philippines

Dr. Ruben Garcia Fabunan
Inventor

For info: 329 N. Vendome Street
Los Angeles, CA 90026
Beeper: (310) 815-6325
Message: (213) 381-2590
Fax: (213) 381-2502

INVENTIONS FOR SALE

1. COBRANIN-FABUNAN INJECTION for

- Snakebite
- Catfish sting
- Other animal poisons:
 - Insect bite/ sting i.e. bee sting
 - Red tide or paralytic shellfish poisoning (PSP)
 - Marine food poison
 - Typhoid fever
 - Malaria

U.S. PATENT # 5, 492, 901 issued February 20, 1996

2. FABUNAN INJECTION VIRAL TREATMENT for

- HIV/AIDS
- Dengue fever
- Influenza

**Other viruses clinically tested at Fabunan Medical
Clinic but not in patent claims:**

- Conjunctivitis (sore eyes)
- Mumps
- Herpes zoster
- Measles
- Hepatitis
- Chickenpox
- Colds
- Rabies (dog bite)

U.S. PATENT APPROVED as of August 2000

**Note: For both PATENTS, the Fabunan injection used for treating
animal poisons and viral diseases have the same GENERIC (USP)
drug components**

CLINICAL RESULTS FOR HIV/AIDS PATIENT TREATED WITH THE FABUNAN VIRAL TREATMENT (Chimpavir-F Injection - CFI)

Patient Information

Initial, Age, Sex and History	Date on which patient tested positive for HIV	Test used to detect HIV	Symptoms prior to start of treatment with the Fabunan Viral Treatment
E.S.B. 47 Female History of blood transfusion; had foreign multiple sex partners.	Patient was first diagnosed in 1996 In preparation for treatment with the Fabunan anti viral injection (Chimpavir-F injection) another test was conducted on May 7, 1999 to confirm that she was HIV positive (St. Luke's Medical Center, Manila, Philippines).	Antibody to HIV I and HIV II (Elisa test) 5/8/99 - <i>reactive</i> (B) 6/20/2000 - <i>reactive</i> (H) Patient had taken a drug cocktail (AZT, Hivid, and Saquinavir) @ 21 capsules/tablets a day for one year (11/1997 - 11/1998), but had to stop treatment due to their high cost.	BP = 122/70 HR = 76/min. Weight = 118 lbs. Occasional cough, constipation, occasional vomiting, skin rashes, skin dryness, multiple dark spots on the skin, depression, insomnia, easy fatigability, weight loss, gastric discomfort, migraine headaches (since 1985), infrequent urination, poor appetite. She was hospitalized for a week in April of 1999 due to acute bronchitis and non-specific dermatitis

Description of Treatment	Results
- Blood was drawn prior to the first injection to obtain information on the patient's CD4 counts. - The pharmaceutical injection was given over a period of 9 days (May 9th - 17th) at 2x per day at the Fabunan Medical Clinic, San Marcelino, Zambales, Philippines. - CD4 results were obtained on May 18th; June 29th; July 30, 1999. - Second treatment series was started on June 5th and the pharmaceutical injection was given one time per week @ 2x each day for four weeks (four treatment days in June). - Third treatment series was started in July and the pharmaceutical injection was given every ten days @ 2x per day (three treatment days in July). - The treatment prescribed 2x each day - twice a month: was repeated for the months of August, September, October, and November. Repeat CD4 testing was done during the first week of December 1999. Overall, after series of Chimpavir-F injections, the patient have not complained of any side effects. <i>Note: Patient, ESB, attended the 13th International AIDS Conference in Durban, South Africa - July 9-14, 2000.</i> (H)	CD4 counts: Coulter flow cytometer - On 5/7/99, initial CD4 value was 287; value on 5/18 was 405; value on 6/29 was 407 (after 2nd injection series); and value on 7/30 was 559 (after 3rd injection series) <i>value on 8/31 was 203; value on 11/30 was 375; value on 6/20/2000 was 244.</i> Succeeding clinical results is seen in video clip. (B) Symptoms (May 17th) Good appetite; good sleep; more normal urination (3x/day); regular bowel movements (2x/day); no more fatigue, headaches, depression, skin rashes gone; weight increase (121 lbs.) (July 30th) Weight increase (128 lbs.); more energy, felt healthier in general. (November 15th) No apparent complaints, very healthy looking; weight is at 128 lbs. <i>Note: the patient relates that she knows HIV-infected individuals who are receiving no treatment and are losing weight with some are experiencing opportunistic infections, & one died.</i> (B)



St. Luke's
Medical Center

INSTITUTE OF PATHOLOGY

278 E. Rodriguez Sr. Boulevard
Cathedral Heights, Quezon City

CERTIFICATE OF HIV TESTING

This is to certify that

whose picture and signature appear below has
been examined for HIV (AIDS) Antibodies.

Printed Name/Signature

St. Luke's Medical Center is
accredited by The Bureau of
Research and Laboratories as
an HIV testing center with BRL
Certificate No. 33.

HIV Screening Test

Performed on: June 20, 2000

Valid until: September 20, 2000

Result:

Reactive

Certified by:

Rosario O. Castillo
Med. Tech. HIV testing

Rafael V. No. Jr.
Pathologist

To Dr. A. G. Fabian
Calif. USA
Fax - (213) 381-2502

INSTITUTE OF PATHOLOGY
CELLULAR IMMUNOLOGY
AND IMMUNOGENETICS LAB.

Flow Cytometry No. I-772
 Doctor: Dr. Fabunan

Age : 48 Sex : F
 Out - patient :
 Date Requested : June 20, 2000
 Date Reported : June 22, 2000

IMMUNODEFICIENCY PANEL REPORT

FLOW CYTOMETRY CLINICAL REPORT

WBC Differential Count	Cells / cu.mm.	%
Lymphocytes (LY)	1452	33
Monocytes (MO)	352	8
Granulocytes (GR)	2596	69
Total Leucocytes	4400	100

Description	Antibody	%	Normal %	Count Cells / cu.mm.	Normal Count Cells / cu.mm.	Gate
Pan T-Lymphocytes	CD 3	48.8	55 - 85	708		LY
T Helper Cell	CD 4	18.8	25 - 50	244 ✓		LY
T Suppressor Cell	CD 8	28.9	25 - 35	420		LY
T Helper / T Suppressor	CD4:CD8	0.6				

Comments:

Decreased total T - cell count and Helper cell count compared to previous study (11-30-99).


 RAVARILIA



St. Luke's
Medical Center

INSTITUTE OF PATHOLOGY

CLINICAL IMMUNOLOGY AND IMMUNOGENETICS LAB

NAME:
AGE: 47 SEX: F
PHYSICIAN: DR.W. FABUNAN

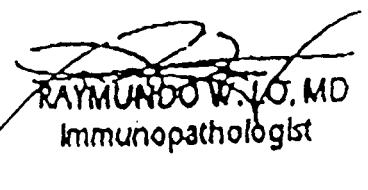
FLOW CYTOMETRY NO. 1675
DATE REQUESTED : 11/30/99
DATE REPORTED : 11/30/99
Out PATIENT:

EPICS XL-MCL ANALYZER
COULTER CYTOMETRY CLINICAL REPORT

WBC Diff.	Cells / Cu.mm.	%
Lymphocytes (LY)	1989	39.0
Monocytes (MO)	408	8.0
Granulocytes (GR)	2703	53.0
Total Leucocytes	5100	100.0

Description	Antibody	%	Normal %	Count	Normal Count	Gate
				Cells / Cu.mm.	Cells / Cu.mm.	
Pan T- LYMPHOCYTES	CD 3	58.19	55 - 85	1157.3		LY
T HELPER CELL	CD 4	18.86	25 - 50	375.1	✓	LY
T SUPPRESSOR CELL	CD 8	31.52	25 - 35	626.9		LY
T HELPER / T SUPPRESSOR RATIO CD4/CD8 0.59						

COMMENTS: Although there is a slight improvement in total T cell and helper cell counts, these are still below the reference range. The helper - suppressor ratio is also slightly improved. Overall, there is minimal improvement in all parameters.


RAYMUNDO W. LO, MD
Immunopathologist



St. Luke's
Medical Center

INSTITUTE OF PATHOLOGY

CELLULAR IMMUNOLOGY AND IMMUNOGENETICS LAB

NAME:
AGE: 47 SEX: F
PHYSICIAN: DR. W. FABUNAN

FLOW CYTOMETRY NO. 1639/64
DATE REQUESTED : 08/31/99
DATE REPORTED : 08/31/99
ROUT PATIENT:

EPICS XL-MCL ANALYZER
COULTER CYTOMETRY CLINICAL REPORT

WBC DIFF.	Cells / Cu.mm.	%
Lymphocytes (LY)	1512	24.0
Monocytes (MO)	567	9.0
Granulocytes (GR)	4221	67.0
Total Leucocytes	6300	100.0

Description	Antibody	%	Count		Normal Count	Gate
			Normal %	Cells / Cu.mm.	Cells / Cu.mm.	
Pan T- LYMPHOCYTES	CD 3	47.4	55 - 85	717		LY
T HELPER CELL	CD 4	13.4	25 - 50	203 ✓		LY
T SUPPRESSOR CELL	CD 8	32.2	25 - 35	487		LY
NATURAL KILLER CELL	CD 56	2.8		423		
T HELPER / T SUPPRESSOR	CD4/CD8	0.4				

COMMENTS: Compared to the study of July 30, 1999, there is a marked decreased in all parameters.

RAYMUNDO W. LO, MD
Immunopathologist

Copy: Dr. Eke F. Wokocha
MARKETING CONSULTANT
Fax(619)463-5438
Tel(619)300-1747 - cell ph.

October 19, 2000

RE: 3 Way Telephone Interview with HIV/AIDS patient

Participants: Dr. Ruben G. Fabunan (Los Angeles, CA)
Dr. Eke F. Wokocha (San Diego, CA)
Patient- Elena "Azon" S. Bejan (MetroManila)

Date : October 16, 2000 Monday

Time 4:15 PM Los Angeles

7:15 AM MetroManila Duration: 12-15 minutes

Briefly, the patient has been under treatment and closely monitored as a case of HIV/AIDS infection at the Fabunan Medical Clinic in the Philippines with start of the Fabunan injection on May 9, 1999.

As related by the patient during the interview, she stated that her last injection was given during the 1st week of July. After that week, she attended the 13th International AIDS Conference at Durban, South Africa on July 9--14, 2000.

On Sept. 15, 2000, she was hospitalized for a few days at the research center in the Philippines as a case of "pneumonia" with no fever and normal white blood cell(WBC) count. No immunology (CD4) test was done due to lack of ingredients.

Questions raised by Dr. Eke on health status, the patient, Elena said that she feels very strong and healthy at that time and she works at an accounting office in MetroManila. She was very happy and excited during the long distance interview. The patient said that she had no maintenance dose of the drug, Fabunan injection("Chimpavir-F inj.") and that she takes only multivitamin pills daily.

Elena said also that her contemporary woman companion who took the AIDS triple drug therapy for one year and without the Fabunan injection died last April 20, 2000 and the other contemporary man who took one year of the triple drug therapy but without the Fabunan injection also died last Aug. 4, 1999 due to AIDS complications.

The patient said that ^{her} weight has not changed since March about 128-130 lbs. when Dr. Fabunan was in the Philippines at that time and was able to meet and treated the patient at the Fabunan Clinic.

Based on the assessment of Dr. Fabunan of the patient condition, being clinically healthy, no complaints and no HIV medications or injections--last injection was 1st week of July....

* Most likely Dr. Fabunan thinks the possibility that the HIV-virus was significantly reduced and controlled. His impression is that---from HIV infection, the patient is now an HIV carrier - as in case similar to Hepatitis virus carrier. More clinical studies has yet to be confirm~~on~~ on FABUNAN injection.

Ruben G. Fabunan, MD
Dr. Ruben G. Fabunan
-Inventor-
Fax(213)387-2502

Copy: Dr EKG WOKUCHA

Ruben P. Fabunan, MD 8/31/00

B R GREENBERG

630 323 1931

00-31-00

12:15

P.01

FACSIMILE TRANSMISSION

From: Barbara R. Greenberg

1409 Burr Oak Road 308A

Hinsdale, Illinois 60521

Phone (630) 323-1807

FAX (630) 323-1931

E-Mail Barbglawyr@aol.com

To: Dr. Ruben Fabunan

FAX number: 213-381-2502

From: Barbara R. Greenberg

Date: August 31, 2000

Number of Pages Including This Page 4

Dr. Fabunan:

Here is the notice of allowance for your patent application. Injection Viral Treatment and a Statement for Legal Services. If you have any questions, please contact me

Sincerely,

Barbara Greenberg

This message is intended only for the use of the individual entity to whom it is addressed and may contain information that is privileged, confidential and exempt from disclosure under applicable law. If you are not the intended recipient, ANY disclosure, copying, distribution, or use of the contents of this transmittal is strictly prohibited. If you have received this transmittal in error, please call this office immediately by telephone so that we may arrange retrieval of the document(s) at no cost to you.

Thank you.

Notice of Allowability

Application No.

09/395,280

Applicant(s)

Fabunan

Examiner

Barbara Badio

Group Art Unit

1816

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to the amendment filed August 14, 2000

☒ The allowed claim(s) is/are 4-11

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(e)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO 892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

Application/Control Number: 09/395,290

Page 2

Art Unit: 1616

DETAILED ACTION

Allowable Subject Matter

1. Claims 4-11 are allowed
2. The following is an examiner's statement of reasons for allowance.

The rejection under 35 USC 103(a) over Bhargava et al. has been withdrawn in light of applicant's amendment filed August 14, 2000. The amendment limits the claimed invention to the treatment of Dengue fever and influenza virus and to the alleviation of symptoms associated with the human immunodeficiency virus. The closest prior art teaches the treatment of herpes simplex/zoster infection (Bhargava et al.). The prior art does not provide motivation to use the composition as claimed by the instant invention.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

STATEMENT FOR LEGAL SERVICES

August 31, 2000

From
Barbara R. Greenberg, Attorney at Law
1409 Burr Oak Road 308A
Hinsdale, Illinois 60521
Phone: (630) 323-1807
FAX: (630) 323-1931
E-Mail: Barbglawyr@aol.com

Issue Fee: Patent: Injection Viral Treatment	\$605.00
Attorney's fee: Phone calls, Faxes to Patent Office	+ <u>30.00</u>

TOTAL AMOUNT DUE: \$635.00

Thank you.

To:

Dr. Ruben Fabunan
329 N-Vendome Street
Los Angeles, California 90026 (By Fax (213) 381-2502)



US PATENT & TRADEMARK OFFICE

PATENT FULL TEXT AND IMAGE DATABASE

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(1 of 1)

United States Patent
5,492,901
Fabunan
February 20, 1996
Cobranin-F injection envenomation antidote

Abstract

An envenomation antidote, and the process for its administration, useful for the treatment of the effects of envenomation resulting from venomous animal bites is disclosed. The antidote consists essentially of a local anesthetic and a glucocorticoid. The antidote is administered in a single dose parenterally through two routes: by subcutaneous infiltration and intramuscular injection, and by direct slow intravenous injection.

Inventors: **Fabunan; Ruben G.** (329 N. Vendome St., Los Angeles, CA 90026)

Appl. No.: **292326**
Filed: **August 16, 1994**
Current U.S. Class:
514/171; 514/829
Intern'l Class:
A01N 045/00
Field of Search:
514/829,171

References Cited [Referenced By]

U.S. Patent Documents

<u>2382546</u>	Aug., 1945	Curtis	424/101.
<u>3504083</u>	Mar., 1970	Philpot, Jr.	424/101.
<u>4012502</u>	Mar., 1977	Philpot, Jr.	424/98.
<u>5053492</u>	Oct., 1991	Rael et al.	530/387.
<u>5089415</u>	Feb., 1992	La Dura	435/269.

Other References

Chemical Abstracts (CA) 105:20187 1986.
CA 88:293469 1987.
CA 89:36586 1978.
CA 97:53142 1982.

Primary Examiner: Killos; Paul J.

Claims

I claim:

1. A method for the treatment of envenomation incidental to the bites of venomous animals including snakes, catfish stings and other venomous animals which comprises the injection of a sterile, liquid composition of a local anesthetic of the ester type and a glucocorticoid.
2. A method according to claim 1 wherein said sterile, liquid composition is administered in two routes: by intramuscular injection and subcutaneous infiltration at, around and above the bite site, and by slow intravenous injection above the bite site or any accessible venous site.
3. A method according to claim 2 wherein said sterile, liquid composition is directly injected intravenously at a rate ranging from about 1 milliliter per 10 seconds to about 1 milliliter per 15 seconds.
4. A sterile, liquid composition used for the treatment of envenomation incidental to the bites of venomous animals including snakes and catfish stings consisting essentially of procaine hydrochloride with epinephrine as the hydrochloride and dexamethasone sodium phosphate.
5. A sterile, liquid composition according to claim 4 wherein is present from about 5 to about 20 milligrams of procaine per milliliter, and from about 4 to 8 milligrams of dexamethasone sodium phosphate per milliliter.
6. A sterile, liquid composition according to claim 4 consisting of procaine hydrochloride, injection, U.S.P. (20 mg/ml), 2% with epinephrine (as the hydrochloride) 1:50,000 and dexamethasone sodium phosphate, injection, U.S.P., 4 milligrams (of dexamethasone phosphate) per milliliter.
7. A sterile, liquid composition according to claim 6 consisting essentially of about 9 parts by volume procaine hydrochloride, injection, U.S.P. (20 mg/ml), 2% with epinephrine (as the hydrochloride) and 1 part by volume dexamethasone sodium phosphate, injection, U.S.P., 4 milligrams (of dexamethasone phosphate) per milliliter.

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a therapeutic composition for the treatment of envenomation incidental to the bites of venomous animals, including snakes, catfish stings and other venomous animals and the process of administration thereof and, more particularly, to therapeutic compositions consisting essentially of a substantially water-soluble, injectable local anesthetic and a water-soluble glucocorticoid injectable, and to the process for administering said composition to the envenomation victim.

2. Description of the Prior Art

Traditional treatment of a venomous snakebite through the use of a serum generated from venom extracted from the particular snake in question is well known as is demonstrated in U.S. Pat. No. 4,012,502 issued on Mar. 15, 1977 to Van B. Philpot, Jr. Philpot's snake venom inhibitor is generated from a material extracted from a snake and subsequently a protein molecule is split and fragments thereof are removed along with unwanted antigenic protein material to thus separate a purified material having high inhibitor activity against snake venom toxicity and proteases. Philpot further discloses a method of purification. However, this is designed as a serum derived from the molecular modification of venom and not an antidote prepared from U.S.P. derived drugs with specific method of administration.

U.S. Pat. No. 3,504,083 issued on Mar. 31, 1970 to Van B. Philpot, Jr. discloses a method of removing the precipitate and thus detoxifying snake serum without destroying the antiplasmin action and properties of snake serum. This antiplasmin action is reported to be useful in human and animal medical procedures to prevent lysis of blood clots. However, this is the modification of a snake serum to retain an antiplasmin agent for medical use other than the treatment of snakebites and the resulting toxins derived from a snake serum and not U.S.P. derived drugs with a specific method of administration.

U.S. Pat. No. 2,382,546 issued on Aug. 14, 1945 to David Curtis discloses numerous developments of other salts of procaine which, when dissolved, in relatively high concentration, in water or glycerine, or glycol, or the derivatives of glycol will serve as media for the dissolution therein of substances which are otherwise insoluble or sparingly soluble in water, glycerine or glycol or the derivatives of glycol. However, this is the development of other salts of procaine and not the use of commonly known procaine as the mechanism of action in the treatment of snakebites and the resulting toxins as a part of U.S.P. derived drugs with a specific method of administration.

U.S. Pat. No. 5,089,415 issued on Feb. 18, 1992 to Frank M. La Duca discloses an improved method of clotting heparized blood utilizing a reagent preparation containing snake venom. This, however, does not disclose a method of treating the victim of a venomous snakebite.

U.S. Pat. No. 5,053,492 issued on Oct. 1, 1991 to Eppie D. Rael et al. discloses a method of utilizing Mojave toxin, a known snake venom toxin, to formulate tumor-specific immunotoxins, capable of attacking tumor cells and destroying tumor cell tissue.

None of the above inventions and patents, taken either singly or in combination, is seen to describe the instant invention as claimed.

SUMMARY OF THE INVENTION

Based on the survey conducted by the World Health Organization, (1954), out of the approximately 500,000 persons who are bitten each year by venomous animals, including snakes, catfish stings and other venomous animals 30,000 to 40,000 die. Other than death, the local effects of envenomation include fang punctures, swelling, discoloration of the skin and pain; whereas, the systemic characteristics include weakness, faintness, nausea, sweating and numbness. Recovery from envenomation is usually prolonged, requiring constant monitoring of the victim's body metabolism due to allergic reactions induces by prior art medications. Thus, it is apparent that an envenomation antidote which quickens recovery from the effects of envenomation would be of great benefit to both physician and patient.

There has always been a certain amount of disagreement over the proper treatment for the effects of envenomation. The most popular, although no longer recommended, prior art method of treatment consists of incision and suction at the bite site accompanied by the application of a tourniquet above the bite site. This method is no longer recommended because its use often results in infection necessitating antitetanus and antibiotic treatment.

The current, almost universal, method for treating the effects of envenomation consists of the administration of either monovalent antivenin or polyvalent crotaline antivenin (hereinafter referred to collectively as "PCA"). PCA is a refined and concentrated hyperimmune equine serum preparation of serum globulins obtained by fractionating blood from healthy horses immunized with the basic antigens in the venoms of all or specific members of the family Crotalidae.

PCA, however, has several disadvantages. Since PCA is an equine-serum based composition, the possibility of serum sickness, pain, muscular weakness, atrophy and anaphylaxis exists throughout the period of its administration. These PCA induced allergic reactions can be severe, and in some cases, the allergic reactions are so severe that the administration of PCA can be fatal. Corticosteroids may sometimes be used to control delayed manifestations of equine-serum allergies resulting from administration of PCA; however, corticosteroids are often ineffective. Thus the physician must balance the risk of death resulting from PCA administration with the risk of death resulting from envenomation.

Further, since PCA is not particularly potent, an enormous multiple dosage volume of PCA must be administered to the victim. Generally, from 20 milliliters to 200 milliliters is administered in multiple doses, with the normal total dosage being 100 milliliters to 150 milliliters. However, it is not uncommon in cases of extreme envenomation for a total of 300 milliliters of PCA to be administered. The World Health Organization has noted that although PCA remains the single most important factor in the treatment of envenomation, it has not reached its recommended potency. Thus, because of widespread sensitivity to PCA, the enormous volume of PCA that must be administered is a significant disadvantage.

PCA is also disadvantageous since injections into fingers, toes or other small extremities are not recommended. These body areas contain terminal arteries, and thus there is not an adequate circulation system for the PCA. In such cases, part of the initial dose of PCA must be injected intramuscularly or subcutaneously at various sites around the limb and above the level of swelling. Unfortunately, this results in not having immediate treatment of the affected area, thereby slowing if not eliminating the therapeutic value of PCA.

depending on the severity of envenomation and on the victims response to PCA. Urine samples must be obtained at frequent intervals for microscopic examination. Skin sensitivity tests must be performed prior to administration of PCA. This is especially important for victims who have a history of allergy or sensitivity to equine-serum. If the skin test is positive, administration of PCA itself can be as fatal as envenomation.

The administration of PCA also has several practical disadvantages. A fairly sophisticated hospital is required due to the required blood, urine and skin testing, and constant monitoring of the victim. Further, PCA is fairly expensive and not readily accessible in developing and underdeveloped countries such as Burma, Africa, India, The Mideast, Latin America, and other Asian countries where the incidence of envenomation is high.

Accordingly, it is a general object of the present invention to provide an envenomation antidote which is potent, which does not induce serious allergic reactions and which can be simply administered in a single, low volume dose.

Another object of the present invention is to provide an envenomation antidote which does not require extensive blood, urine or skin tests.

It is still a further object of the present invention to provide an envenomation antidote which is capable of being inexpensively produced for immediate use and is readily available in local hospitals of underdeveloped and developing countries.

These and other objects of the present invention will become readily apparent upon further review of the following specifications.

BRIEF DESCRIPTION OF THE DRAWINGS

There are no figures or drawings in this case.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT(s)

The present invention is an envenomation antidote useful for the rapid treatment of envenomation by venomous animals including snakes, catfish stings and other venomous animals. The antidote is prepared from U.S.P. derived drugs and is administered parenterally in two simultaneous routes: by subcutaneous infiltration and intramuscular injection and by intravenous injection.

The antidote consists essentially of a water-soluble local anesthetic and a glucocorticoid. The term local anesthetic refers to procaine hydrochloride injection, U.S.P. with epinephrine (as the hydrochloride). Procaine hydrochloride is the preferred local anesthetic of the ester type as it is the least toxic of other known local anesthetics. However, since procaine hydrochloride produces vasodilation, a vasoconstrictor such as epinephrine is added to the procaine hydrochloride to reduce the vasodilating effects and consequent rapid removal of procaine hydrochloride from the site of infiltration and injection.

The operative amount of the procaine in the local anesthetic in aqueous solution ranges from about 5 to about 20 milligrams of procaine per milliliter of the local anesthetic. Preferably, the local anesthetic is the commercially-available procaine hydrochloride, injection, U.S.P. (20 mg/ml), 2% with epinephrine (as the hydrochloride) 1:50,000.

The term glucocorticoid refers to dexamethasone sodium phosphate. The operative amount of the dexamethasone sodium phosphate in the aqueous dexamethasone sodium phosphate solution ranges from about 4 to about 8 milligrams per milliliter. Preferably, the glucocorticoid is the commercially-available dexamethasone sodium phosphate, injection, U.S.P., 4 milligrams (of Dexamethasone phosphate) per milliliter.

The dosage of the antidote depends upon several factors including age, weight, sex, severity of envenomation and the response to treatment. The dose of the antidote ranges from about 5 milliliters to about 20 milliliters. Generally, a typical 39 year old, 120 pound male, having severe envenomation from snakebite is administered a total of 20 milliliters of the antidote.

The antidote is prepared by sterilely transferring the procaine hydrochloride with epinephrine solution and the dexamethasone sodium phosphate solution into a sterile syringe followed by gentle mixing. Prior to use, syringes and needles should be sterilized, preferably commercially available sterile syringes and needles should be used.

The operative amount of procaine in the antidote ranges from about 5 to about 20 milligrams per milliliter, and the operative amount of dexamethasone sodium phosphate in the antidote ranges from about 4 to about 8 milligrams per milliliter. Preferably, the volume ratio of procaine hydrochloride, injection U.S.P., 4 mg. (of dexamethasone phosphate) per ml is 9 to 1. Thus in 10 milliliters of the preferred antidote solution, as set forth in Example 1 below, there is present essentially about 180 milligrams of procaine, and about 4 milligrams of dexamethasone sodium phosphate. This solution can be stored for at least 2 years.

The following example describes the manner and process of making and using the invention and sets forth the best mode contemplated by the inventor of carrying out his invention but is not to be construed as limiting. For example, other commercially available formulations of procaine hydrochloride with epinephrine and dexamethasone sodium phosphate may be used provided the amounts of these ingredients are maintained in the operative ranges set forth above.

EXAMPLE 1

1 syringe containing 10 ml of the sterile antidote is prepared as follows:

milliliters
Procaine hydrochloride, injection,
9
U.S.P. (20 mg/ml), 2% with epinephrine
(as the hydrochloride) 1:50,000
Dexamethasone sodium phosphate,
1
injection, U.S.P., 4 mg (of
dexamethasone phosphate) per ml.

The above ingredients are aseptically transferred into a sterile 10 milliliter syringe. After the ingredients

are gently mixed, the antidote-containing syringe is ready for administration.

For parenteral administration, two identical antidote-containing syringes are prepared, each syringe containing an equal volume of the antidote, are prepared.

The administration of the antidote, unlike PCA, is quite simple and does not require extensive skin, blood or urine testing prior to its administration. The only testing that should be made is for allergic reaction to the procaine hydrochloride; however, such reactions are very rare.

One of the two syringes prepared as described above is used to administer the antidote parenterally by subcutaneous infiltration and intramuscular injection at, around and above the bite site in order to serve as a (blocking tourniquet). Generally, a "ring" method is commonly employed in which small urticarial wheals are formed around and above the bite site and subsequently connected by infiltration with the antidote. This first syringe is also used to administer the antidote intramuscularly at and around the areas of subcutaneous infiltration. Again, unlike PCA, use of the infiltration method allows administration of the antidote to toes, fingers and other small extremities.

Simultaneous with administration of the antidote by subcutaneous infiltration and intramuscular injection, the second syringe, prepared as described above, is used to administer the antidote parenterally by direct slow intravenous injection above the bite site or any accessible venous site. The antidote in the second syringe is injected intravenously at a rate ranging from about 1 milliliter per 10 seconds to about 1 milliliter per 15 seconds, preferably 1 milliliter per 15 seconds. Use of the well known butterfly needle method has been found most successful for the direct slow intravenous injection.

It can be seen from the above description that the present invention provides a readily available envenomation antidote which is useful for the treatment of envenomation incidental to venomous animal bites including snakes, catfish stings and other venomous animals. By combining two U.S.P. derived drugs, an envenomation antidote is formulated which can be simply administered in a single, low volume dose. Unlike the prior art method of treating envenomation, extensive blood, urine or skin tests are unnecessary. The invention provides the further advantage of allowing effective use of the antidote when the bite is located on fingers, toes and other small extremities. Furthermore, due to the inexpensive, readily available ingredients, the invention can be used in the rudimentary hospitals of underdeveloped countries envenomation is highly prevalent.

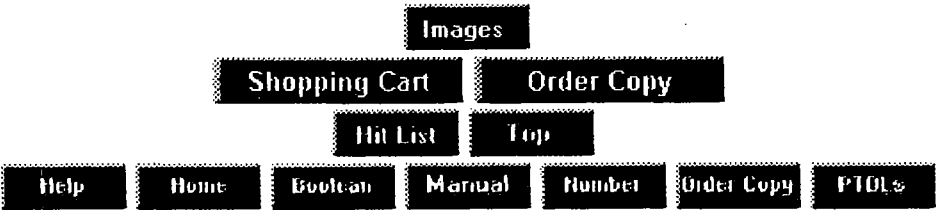
MEDICAL EXPERIMENTATION AND APPLICATION

From Sep. 19, 1975 to Sept. 21, 1975 Mr. Santiago Raguindin of Linasin, San Marcelino, Zambales, Philippines was under medical treatment in San Marcelino Emergency Hospital by Dr. Ruben G. Fabunan due to snakebite injury. In a single blind trial experiment, after an informed consent from the victim's wife, Mrs. Rosario Raguindin, the formulation aforementioned was initially administered parenterally at San Marcelino Emergency Hospital to snakebite victim, Santiago "Ago" Raguindin, 39, male, farmer, about 120 lbs. nearing his grave from the effects of the snake venom of a cobra, on Sep. 19, 1975. The injection was given with great care and confidence in a single dose. Although the popular method of first aid treatment of incision and suction at the bite site and tourniquet applied above the bite site and other snakebite measures were given by previous physicians to the victim, his condition deteriorated progressively. Commercial antivenins were not readily available at this rural hospital. Physical examination revealed unstable vital signs with blood pressure at 130/100; temperature at 36.6 degrees C., and a weak, irregular pulse. Two fang marks with oozing dark bluish blood at the dorsal aspect of the

right hand with progressive edema of that extremity. Systemic manifestations of moderate to severe envenomation included blurred vision, apprehension, slurred speech, dysphagia, profuse sweating, excessive whitish sticky sputum, discoloration of the skin, acute respiratory distress and lethargy.

The aforementioned drug of the present invention was administered as previously prescribed. About 2-5 minutes after completion of the intravenous route, drug related adverse effects were noted like transient apprehension, confusion, tachycardia, sweating, complaint of thirst and fatigue with gradual response within an hour to progressive recovery. The patient remains in good health without hand deformity. Thus, the first treatment of a patient ready to expire within hours and returned to perfect health through use of the present invention and the prescribed method of administration. This is a documented account of the experimental administration and not a commercial offering of the aforementioned treatment, see attachment A.

It will be understood by those skilled in the art that the present invention is not limited to the sole embodiment described above, but encompasses any and all embodiments within the scope of the following claims.



Commercialization Aspect

Market Potential

A. Description of Potential Markets

On a global scale, the market potential for the treatment of illnesses (e.g., snakebites and dengue fever) caused by animal toxins with Dr. Fabunan's antidote and viral treatment is considerable for the following reasons:

- 1) Current lack of effective treatments, other than supportive intervention, for many animal-toxin induced illnesses (i.e., little competition with other pharmaceuticals).
- 2) The immense number of individuals (estimated at 2.5 billion) who are at risk for acquiring dengue fever and its particularly serious forms of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) and therefore would be candidates for treatment with the viral treatment.
- 3) Potential applications to other animal toxin-induced illnesses.

The primary markets for both the antidote and viral treatment would be less-developed or Third World emerging countries. The viral treatment in particular has a potentially very broad geographic appeal. For example, as of 1997, countries representing all continents, except Europe, have reported cases of dengue fever activity. For North America and South America, these countries include Mexico, the Caribbean Islands, Honduras, Nicaragua, Venezuela, Colombia, Peru, and Brazil. For Asia, all countries including India, Indonesia, Bangladesh, and Pakistan have reported outbreaks. Even though no major outbreaks have occurred, the southeastern part of the United States is considered an area of risk for epidemic dengue fever due to its subtropical/tropical climate. For Africa, the illness has primarily appeared in countries located on the border of or south of the equator and bordering either the Indian or Atlantic Oceans. However, countries located in central Africa are also considered at risk for epidemic dengue fever. In Australia, the illness to date has been confined to the northeast corner.

The following 1998 newspaper articles attest to the vast numbers of individuals who are suffering from dengue fever on a yearly basis:

Dengue Fever Cases Nearly Double in Vietnam Manila Bulletin 5/98

SEA Grapples with Dengue Fever Surge Philippine Star 5/98

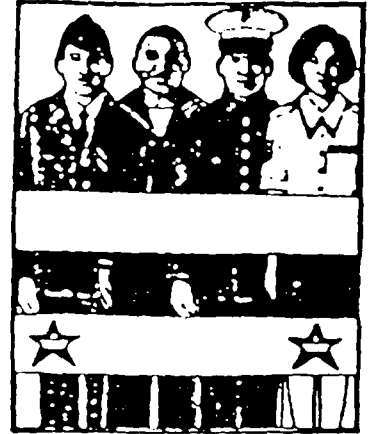
Dengue Fever Leaves a Trail of Death Philippine Daily Inquirer 8/98

Dengue Cases Seen To Hit 72,000 in the Philippines This Year LA Asian Journal 9/98

Facing the Dengue Epidemic California Examiner 9/98

Storm Deluge Lingers Over Central America New York Times 11/98

Another potential market for both the antidote and viral treatment is the armed services or military. The military has a vested interest in maintaining the health of its men and women. Thousands of U.S. soldiers who fought in the Pacific in World War II died of malaria. During the Vietnam War, the U.S. Army invested a large amount of money in malaria drug development. It is thus conceivable that the military in both the U.S. and other countries would be interested in the antidote and viral treatment for their potential uses in treating the several animal toxin-induced illnesses to which military personnel serving overseas might be exposed.



Historically, little effort has been expended by pharmaceutical companies on the development of drugs or vaccines for illnesses that are rampant in less-developed countries. For example, the world has been waiting for years for an effective treatment for malaria, a leading killer of the world's poorest people. Yet, to date there is still not an effective treatment for malaria. Why? Because the development of new drugs is a very expensive, time-consuming undertaking. In the case of malaria, pharmaceutical companies have felt that they would never recover their investment in drugs developed for less-developed countries let alone make a profit. Also, the lack of effective distribution channels in many less-developed countries has been viewed as a major obstacle to commercialization.

B. The Characteristics of the Cobranin-F™ Antidote and Fabunan Viral Injection Treatment and Their Potential Impact on Successful Commercialization

Given the fact that the main markets for the antidote and treatment would be less-developed and Third World emerging countries, it would appear that the antidote and viral treatment would not be an attractive investment opportunity from a pharmaceutical company's perspective. However, both the antidote and viral treatment exhibit several characteristics that could conceivably allow the patent licensee to:

- *recoup its investment in a reasonable amount of time.*
- *make a profit.*
- *make a positive difference in the lives of individuals who have often been "forgotten" by industrialized countries.*

Even though commercialization-related activities conducted by the patent licensee should be relatively straightforward through the clinical trial stage, successful commercialization will ultimately be dependent upon a successful distribution strategy for the "less developed/Third World emerging countries" markets. In contrast to previous decades, many pharmaceutical countries today have a global presence, thereby increasing their probability of developing effective distribution strategies for the aforementioned markets. Effective distribution of pharmaceuticals to less-developed/Third World emerging countries could, however, be strongly linked to the political and economic stability of the regions. Therefore, the company which licenses the rights to the antidote and viral treatment should plan to work closely with the World Health Organization, the International Red Cross, and local governments to help ensure that:

- 1) *the pharmaceutical treatments will reach the intended populace.*
- 2) *sufficient information is provided to physicians.*

Commercialization-Related Characteristics of the Cobranin-F™ Antidote and
Fabunan Viral Injection Treatment

Antidote/Therapy Property	Comments	Impact on Commercialization Costs Relative to Commercialization Costs for a Brand New Drug
Actual drug discovery will not be required.	The two FDA-approved generic drugs used in the antidote and therapy are well-characterized.	Substantial reduction due to the fact that little, if any, R&D will be required.
The inventor envisions that the antidote and viral treatment would be sold as sterile solutions in pre-filled syringes. Each syringe would contain the volume of solution required for one injection. This type of packaging would make the product user-friendly for both field military doctors as well as physicians in less-developed countries.	Sterile syringe filling is an established technique.	If the patent licensee already has the capability of sterile syringe filling as well as the required capacity for filling the antidote/therapy, no new manufacturing equipment would be required.
Stability information of the individual drugs used in the antidote and treatment is available. The antidote does not contain proteins.	This means that there should be no stability "surprises" for the antidote. Nevertheless, as with all "new" formulations, "final container" stability data would have to be collected to verify the predicted stability of the antidote and treatment at the specified storage temperature. The fact that the two formulations do not contain proteins implies that they might not require storage at 2-8°C or lower temperatures.	Existing procedures for monitoring the stability of the individual drugs could be used, thereby eliminating the need for development of new procedures and/or stability models. The temperatures used in the study should reflect the possible temperatures to which the formulation would be exposed in "real" settings in less-developed/Third World emerging countries.
Encouraging preliminary patient treatment results for snakebites, dengue fever, and red tide poisoning.	The limited clinical data collected to date on humans suggests that the antidote may cure a statistically significant number of individuals exposed to certain animal toxins. Additional data continue to be collected at the Fabunan Clinic in the Philippines.	Additional clinical data as per a formal clinical trial study conducted by the patent licensee would be required prior to commercialization of the antidote and viral therapy. Higher clinical trial costs than usual may be incurred if the studies are conducted in target geographic markets. However, availability of sufficient amounts of the antidote for thorough evaluation should not be an issue. Also early compelling results obtained in formal field trials may result in "early" regulatory approval of the antidote and viral therapy and thereby speed up their market release dates.
The treatment costs (from admittance to release) incurred by the Fabunan Clinic have been less than \$10/patient for both snake bite and dengue fever victims when the drugs were purchased at whole sale prices.	The cost of treating snakebite victims is lower with the antidote relative to snake antivenom. In addition, the victims do not require pre-testing to determine if they are allergic to horse serum, the medium from which antivenoms are derived. The cost of treating dengue fever patients with the viral therapy is lower than the costs generally associated with supportive therapies such as I.V. solutions, or in the case of DHF, blood transfusions.	The lower treatment costs relative to existing therapies makes both the antidote and viral treatment potentially attractive drugs for use in countries which do not have well-developed economies capable of supporting expensive health care systems.

Synopsis

Synopsis

The potential advantages of the Cobranin-FT[™] Antidote and the Fabunan Viral Injection Treatment as therapies for illnesses caused by many animal toxins can be summarized as follows:

- *Lower than usual commercialization costs since they contain readily available generic drugs.*
- *No unusual side effects.*
- *Offer a method for treating illness for which no specific treatment is currently available (e.g., dengue fever).*
- *Lower patient treatment costs relative to existing therapies.*
- *Ability to treat several types of animal toxin-induced illnesses.*
- *For venomous snakebite victims, eliminates the risk of adverse reactions to antivenin.*
- *For dengue hemorrhagic fever patients, may eliminate the need for blood transfusions, thereby eliminating the risk of transmission of HIV or Hepatitis viruses to patients.*
- *Ease of use (pre-filled syringes).*
- *Considerable market size on a global scale (military organizations as well as the general populace).*

Although they consist of FDA-approved generic drugs, the antidote and viral treatment represent new pharmaceuticals due to the apparent synergistic effects of the drug components when used in combination. Preliminary clinical results suggest that the antidote and viral treatment have the capability of curing a number of animal toxin-induced illnesses.

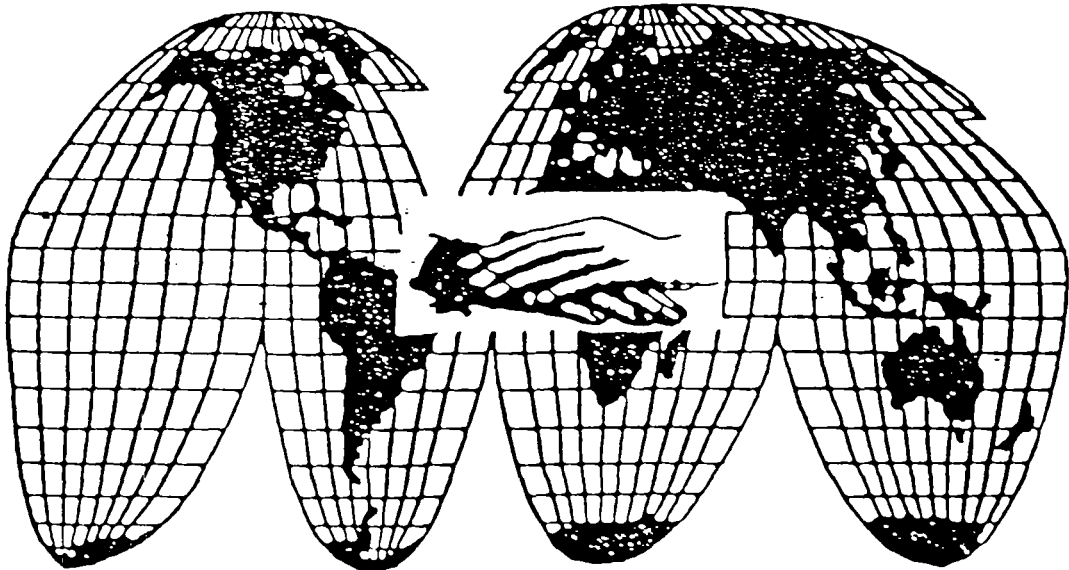
Relative to brand new drugs, commercialization of the antidote and viral treatment would probably be associated with a lower degree of risk from a technical perspective but a higher level of risk from a distribution perspective. The primary technical risk is that statistically significant results may not be obtained in formal clinical trial studies. Such "negative" results, can, however, occur with any new drug especially if the drug was developed using an animal model. The fact that compelling results have been obtained with actual patients and not animals implies that the antidote and viral treatment should both "work" in a statistically significant number of cases during formal clinical studies.

The distribution risk is that the populace (individuals or government-sponsored health care systems) in target market countries may not be able to afford the antidote/viral treatment at a cost that allows the patent licensee to make a profit. However, the projected treatment costs of the antidote US \$10/inj. are believed to be accurate and should thus be significantly lower than the costs associated with current treatments. This feature should make the antidote/viral treatment a cost effective alternative for many "poorer" countries.

In addition, it must be emphasized that dengue fever, in particular, is a global illness. The countries in which epidemic outbreaks of this disease have occurred range from "rich" countries (e.g., Australia) to very poor countries (e.g., Bangladesh). It is conceivable that the antidote/viral therapy could be sold for higher prices in richer countries and lower prices in poorer countries to achieve reasonable profit-bearing revenues for the patent licensee.

Another potential distribution risk is that many less-developed/Third World emerging countries do not have a strong healthcare network (e.g., drug stores, well-equipped hospitals, etc.) All individuals often seek treatment at rural clinics. This situation could make it difficult to get the antidote/viral therapy into the hands of physicians. For these countries, it is highly likely that the World Health Organization and/or the International Red Cross would be very willing to work with the patent licensee to make the antidote readily available in rural settings.

Finally, the procurement of the patent rights to the antidote, viral treatment, and other potential applications would provide the licensee with the opportunity to engage in a humanitarian effort to improve the healthcare of thousands of individuals worldwide. This global-oriented mission will most certainly lead to considerable patient, relief agency, health care worker, and governmental goodwill towards the patent licensee.



August 24, 2000

CERTIFICATION

To whom it may concern:

This is to certify that Dr. Eke F. Wokocha and associates is the authorized marketing consultant for the Outright Sale of the following patents namely:

- 1) US patent # 5,492,901 issued on Feb. 20, 1996
Cobranin-Fabunan injection- antidote for snakebite,
catfish sting and other animal poisons i.e.
malaria, typhoid fever, red tide
- 2) US patent- approved as of Aug. 2000
Fabunan injection viral treatment for
HIV/AIDS, Dengue and Influenza

That - the promising drug therapy manual for the above inventions was scientifically and accurately prepared by the undersigned inventor with the cooperation of a feasibility analyst.

Videoclip of HIV/AIDS patient is also available for presentation.

Thank you.

Sincerely yours,

Ruben G. Fabunan, MD
Dr. Ruben G. Fabunan
329 N. Vendome St.
Los Angeles, CA 90026
Tel (213) 381-2590
Beeper (310) 815-6325
Fax (213) 381-2502

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Inventor's Profile

INVENTOR'S BACKGROUND

RUBEN GARCIA FABUNAN, MD

Birthplace: San Marcelino, Zambales, Philippines
Date of Birth: March 15, 1945
Parents: Roman B. Sr. and Feliza G. Fabunan
Elementary: Valedictorian, San Marcelino Elementary School
San Marcelino, Zambales, Philippines 1957
High School: First Honorable, Olongapo Provincial (Jackson) High School
Olongapo City, Zambales, Philippines 1961
College: Entrance Scholar, Bachelor of Science (Pre-Med)
University of the Philippines
Diliman, Quezon City, 1965-66
Graduated: Doctor of Medicine –
SouthWestern University Matias H. Aznar
Memorial Medical School
Cebu City, Philippines 1973
Marital Status: Married with three children
Citizenship: Filipino-American

Work Experience:

- Independent Medical Researcher/ General Medicine, 1975 to date
- Founder – Fabunan Medical Clinic, San Marcelino, Zambales, Philippines, 1975
- Contract Medical Worker, Government of Iran, 1976-1979

Inventions:

- Envenomation Antidote: Snakebite, Catfish Sting and other animal poisons –
US Patent No. 5,492,901
First Place Award in Biotechnology, "Poison Antidote", Invention Convention,
1997, Pasadena, California, USA
- Fabunan Injection Viral Treatment for AIDS, Influenza, Dengue (US Patent approved–Aug.2000)
- Monitor Diaper – US Patent D 358,779
- Dr. Shoe Boy Driving Footguard – US Copyright 1985, 1992

Organizations:

- Life member, Philippine Medical Association, 1974 to date
- Honored member, Who's WHO of American Inventors, 1998-1999
- Lifetime member, American Society of Patent Holders (ASPH),
National Inventors Hall of Fame, Ohio, USA, 1997 to date

Clinical Drug Investigators:

OSCAR G. FABUNAN, MD
Clinical Acupuncturist, General Medicine
University of the East-Ramon Magsaysay Memorial Medical Center,
Metro Manila, 1974

WILLIE G. FABUNAN, MD
Clinical Acupuncturist, General Medicine
Cebu Doctors' College of Medicine, Cebu City, Philippines 1981

ROMAN G. FABUNAN, Jr., MD
Anesthesiologist
Manila Central University College of Medicine, Metro Manila, 1985

FABUNAN MEDICAL CLINIC - San Marcelino, Zambales C – 2207 Philippines
A Family Medical Group - Drs. Annie, Linda, Agnes, Nida Fabunan

RGF '99

Ruben G. Fabunan MD

Issue Date
February 20, 1996

Patent Number
5,492,901

Dr. Ruben Garcia Fabunan

INVENTOR
COBRANIN-FABUNAN INJECTION
ENVENOMATION ANTIDOTE FOR SNAKEBITE AND CATFISH STING

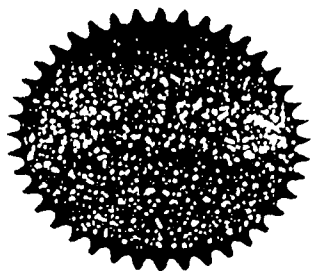
The Commissioner of Patents and Trademarks has received an application for a patent for a new and useful invention. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Bruce Lehman
Commissioner of Patents and Trademarks



First Place Award

Is Presented to

Dr. Ruben G. Fabunan

*In the Category of
Biotechnology*

*For the Invention of
Poison Antidote*

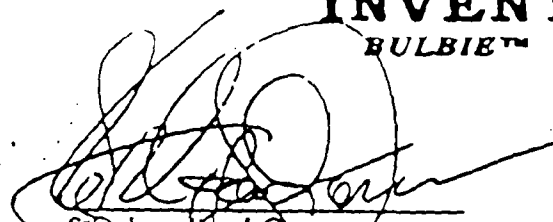
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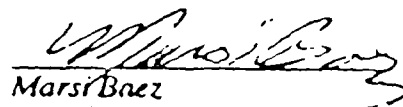
INVENTION CONVENTION®

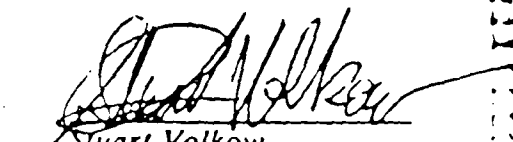
BULBIE™ & INVENTIONS AWARDS CEREMONY

August 31, 1997

Pasadena, California USA


Stephen Paul Grass
Founder, President and CEO


Marsi Baez
Vice President


Stuart Volkow
Awards Chair

AMERICAN SOCIETY OF PATENT HOLDERS



This is to certify that:

Ruben García Fabunan, M. D.

is a member of the American Society of Patent Holders,
an organization that recognizes technical achievement through
Inventure Place, Home of the National Inventors Hall of Fame.

U.S. Patent No. 5,492,901

Title: Cobranin - Fabunan Injection Animal
Poison Antidote



0172



APPLICATION NUMBER	PATENT NUMBER	ISSUE DATE	ATTORNEY DOCKET NO.
08/292,326	5492901	02/20/96	

Title: Cobranin-Fabunan Injection Envenomation Antidote
2901 for snakebite and catfi 7707 sting

RUBEN G FABUNAN
329 N VENDOME ST
LOS ANGELES CA 90026

The Commissioner of Patents and Trademarks

*Has received an application for a patent
for a new and useful invention. The title
and description of the invention are en-
closed. The requirements of law have
been complied with, and it has been de-
termined that a patent on the invention
shall be granted under the law.*

Therefore, this

United States Patent

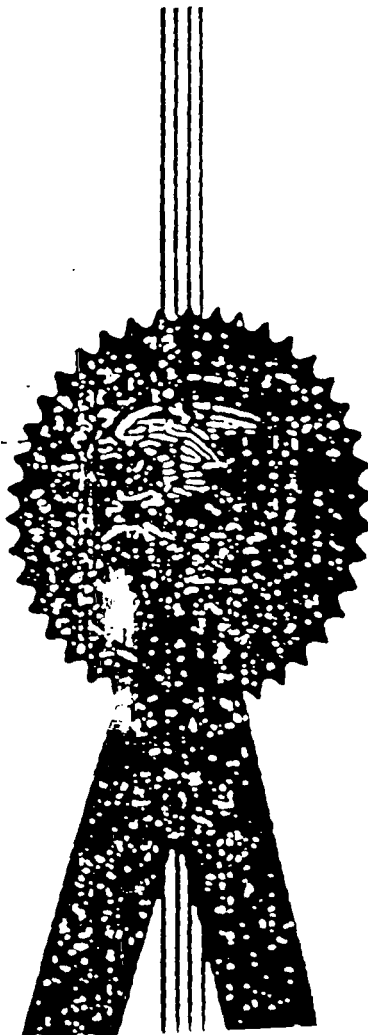
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title to this patent the right to exclude
others from making, using or selling the
invention throughout the United States
of America for the term of seventeen
years from the date of this patent, sub-
ject to the payment of maintenance fees
as provided by law.*

Bruce Lehman

Commissioner of Patents and Trademarks

Kenneth J. Casper

*The
United
States
of
America*



WHO'S WHO OF AMERICAN INVENTORS

1998-1999 Edition

Robert B. Faberman, M.D.

**Who's Who of American Inventors
Hooper Group Publishing
PO Box 86003
Baton Rouge, LA 70879**

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**WHO'S WHO of AMERICAN INVENTORS
1998-99 Edition**

ISBN: 0-929956-12-5

DREW ERICSSON

PO Box 6211

Gulf Breeze, FL

Gulf Marine Institute of Technology, President

Patent Number: 5628280

Oyster Cleansing/Purification Array

An oyster and other molluscan cleansing system suitable for purifying or promoting the grow out of, for example, oysters, clams, mussels, or the like

Joseph Peter Errico

150 Douglas Rd.

Far Hills, NY

Self-employed, Inventor

Patent Number: 5543187

Amorphous Metal - Ceramic Composite Material

A composite material comprising a multilaminate structure of amorphous metal and ceramic layers which may be used for structural and/or electrical purposes

Robert A. Ersek, M.D.

630 W. 34 St.

Austin, TX

Personique-Plastic Surgery, Chairman

Patent Number: 5258028

Micro Implants

Microspheres of 80-500 micron suspended in a water soluble gel injected to build bulk for plastic surgery

Freddie B. Erwin

1928 South Main St.

Malvern, AR

Fred's Glass and Body Shop, Owner

Patent Number: 5640876

Locking Pliers Pulling system

Can be used for stretching metal in body and fender shops; also for a fence stretcher and many other ways

Rene Daniel Esser, M.D.

881 Lurline Dr.

Foster City, CA

M.D.

Patent Number: 5601550

Pelvic Pin Guide System

Allows for easy and fast insertion of pins into iliac bones and montage of an external fixator to reduce fracture displacement, and to control internal bleeding

Chuck A. Evans

743 Wilson Blvd.

Central Islip, NY

Patent Number: 5683022

Multi Pouch Belt

The belt that you can change the pouches to carry different things; such as phone, keys, water bottle, gum, pens, eyeglasses etc. and a hidden money pouch

Earl Wayne Eversoll

325 S. Wickiup

Apache Junction, AZ

Glacier Vending Service, Route Technician

Patent Number: T2356

Jeep Carrier

Fits on spare tire of off road vehicle, unfolds containing tie down straps; when opened makes shelf to carry a five gallon water cooler

James Faasel

1946 Martindale S.W.

Wyoming, MI

Retired

Patent Number: 5667118

Front Mount Panniers Rack

Clamps to most forks, even those with shocks; mounts faster than others, and no tools are needed

✓ **Ruben Garcia Fabunan, M.D.**

329 North Vendome St.

Los Angeles, CA

Fabunan Medical Clinic of the Philippines,

Physician/Inventor/Medical Scientist

Patent Number: 5492901

Cobranin-Fabunan Injection Envenomation Antidote

Antidote for poisonous snakebites, catfish sting, insect bite or sting, dengue fever, red tide, paralytic shellfish poisoning and marine food poisoning, *malaria, typhoid fever*

Curtis Edward Falle

3559 Mining Rd.

Kershaw, SC

Bowater Carolina, Maintenance or Millwright

Patent Number: 5524779

Safety Closure for a Container

Container which is not easily removed by children, no additional tools needed, little physical effort required to remove, inexpensive to manufacture

Steven Michael Falcaro

1741 Bramar Ave.

Fort Myers, FL

Maritime Technologies Corp / New Vibrations Inc., V.P. of R&D/ President

Patent Number: 5465676

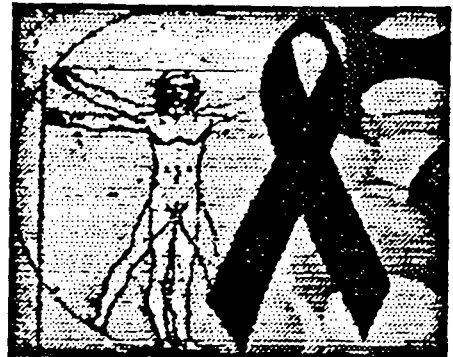
Barnacle Shield

Doctors describe AIDS patients' medical paradox

September 19, 2000

Web posted at: 3:05 PM EDT (1905 GMT)

WASHINGTON (Reuters) -- Some AIDS patients whose ravaged immune systems have been boosted by taking cocktails of powerful medicines have been suffering a surprising increased susceptibility to infections, researchers said on Monday.



Scientists at Thomas Jefferson University in Philadelphia, Pennsylvania, labeled as a medical paradox their discovery that AIDS patients whose conditions had been improving thanks to treatment with drug cocktails had been coming under attack from opportunistic infections that ordinarily should not have been much of a problem.

In a study published in the journal *Annals of Internal Medicine*, the researchers said the sometimes-fatal "immune reconstitution syndrome" stemmed from an inflammatory reaction by the newly strengthened immune system to bacteria or viruses already present in the patient.

The researchers said the causes of the syndrome were unknown.

The researchers said they were startled by the fact that the infections were affecting patients who had been benefiting from so-called highly active antiretroviral therapy (HAART) involving the use of combinations of powerful anti-HIV (human immunodeficiency virus) medicines.

The doctors described learning of patients with a typical infection suffered by those with HIV -- *Mycobacterium avium* infection.

"The infection was not showing up in someone with end-stage AIDS who wasn't taking antiretrovirals and HAART, but someone getting better and on HAART," Thomas Jefferson University's Dr. Joseph DeSimone said in a statement.

DeSimone said some doctors give antibiotics to treat the opportunistic infections, while others prescribe anti-inflammatory drugs. Some doctors reduce the HAART treatment.

"No one is exactly sure what to do against this syndrome yet," DeSimone said.

The study concluded that it would be difficult to form controlled studies to find suppressing agents given the "atypical and sporadic presentation of these reactions" considering the number of patients using drug cocktails.

More than a year ago, researchers began to see patients with HIV, the virus that causes AIDS, developing infections at times that caught them off guard. The Jefferson doctors said they decided to search the medical literature and speak with colleagues to learn whether others had seen similar developments.

They said doctors at other hospitals mentioned infections such as CMV retinitis, an AIDS-related blindness.

"The AIDS-related blindness some patients experience was getting better, and when patients were started on their HAART therapy they overall were getting better," said Dr. Timothy Babinchak, clinical director of infectious diseases at Thomas Jefferson University Hospital.

"But then they seemed to be getting an aggravation of their disease. It was another process, not necessarily the CMV being reactivated. It was an inflammatory reaction to the CMV infection already there."

HOME

Sub-Saharan Africa



HIV/AIDS

Intensifying Action Against HIV/AIDS in Africa

- AIDS is now the leading cause of death in Sub-Saharan Africa (SSA). Since the epidemic began, the

estimates that **14 million** Africans have died from AIDS. In 1999, **23.3 million** Africans were estimated to be living with the disease, **3.8 million** of whom were infected with HIV during that year, and a total of **10.7 million** children were estimated to be orphaned by it in this region alone.

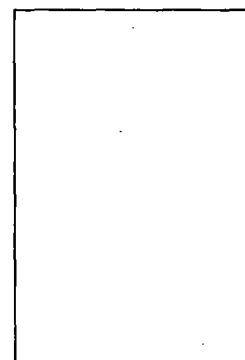


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- The 21 countries with the highest HIV prevalence in the world are in Africa. In Botswana and Zimbabwe, one in four adults is infected. In at least 10 other African countries, adult prevalence rates exceed 10 percent.
- The strategic plan introduces the World Bank's new response to the epidemic in partnership with African governments and



SEARCH

FEEDBACK

SITE MAP

SHOWCASE





WHY THIS ISSUE ?

[HOME](#) [WHAT'S NEW](#) [SITE MAP](#) [DISCUSSION LIST](#) [CONTACTS](#) [LINKS](#)

African Development Forum 2000

AIDS: The Greatest Leadership Challenge

[Objectives & Aims](#)

[Expected Outcomes](#)

[Conference Themes](#)

[ECA's Role](#)

[ADF - a process](#)

[Partnerships](#)

[Follow-up Mechanisms](#)

[Exhibition](#)

[Discussion List](#)

[Conference Programme](#)

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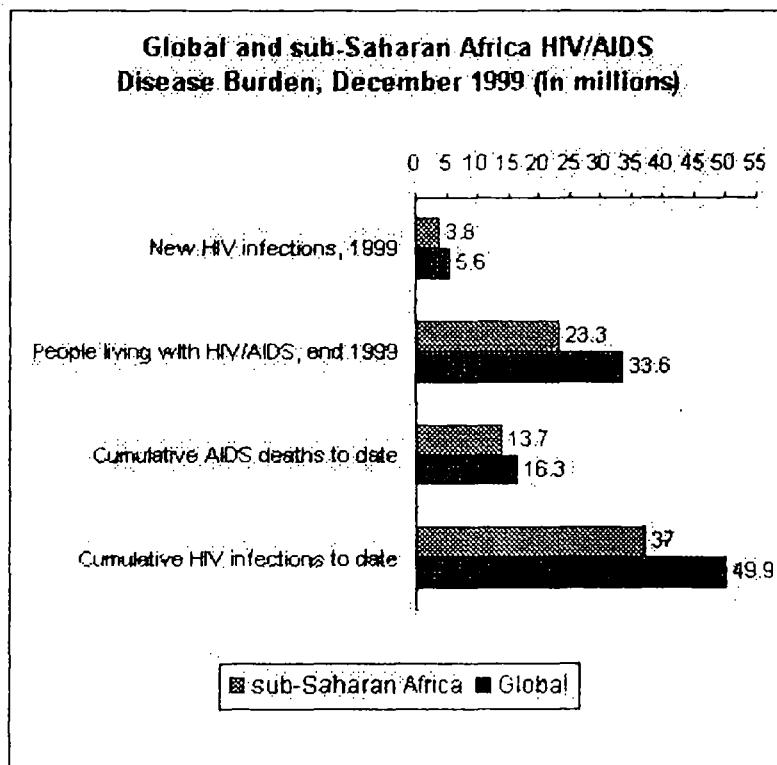
[Hotel Information](#)

[General Information](#)

[Home](#) > [About ADF 2000](#) > Why this issue for the second ADF?

This year's ADF theme on **"AIDS: the Greatest Leadership Challenge"** is unique because it offers an opportunity to conduct critical appraisal of current strategies and approaches and to discuss how to secure the commitment of African leaders to take action now to implement prevention and care programmes.

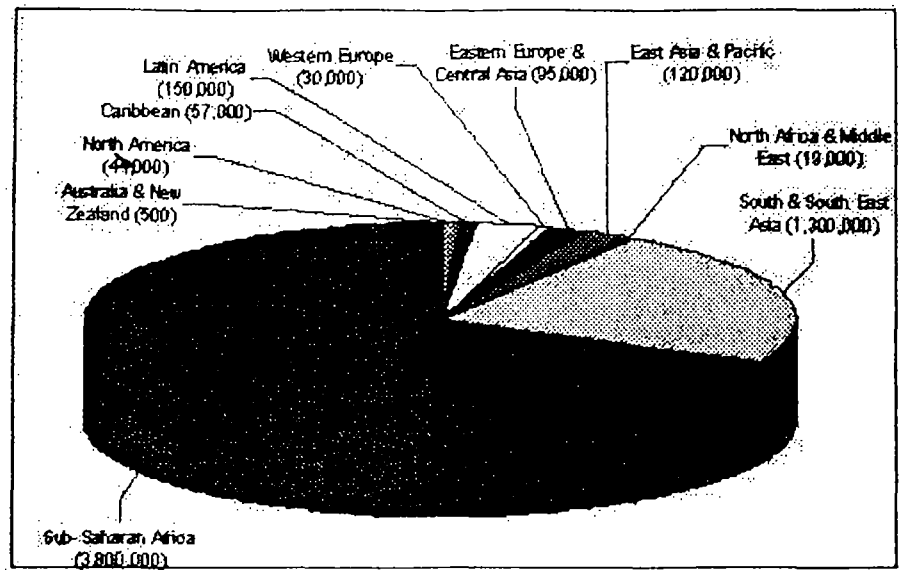
The HIV/AIDS epidemic is taking a devastating toll in terms of human suffering; it is jeopardizing economic growth, development prospects and political stability, especially in sub-Saharan Africa (SSA). Given the degree to which HIV/AIDS is undermining progress in development, it is no longer merely a health problem, but poses a major development crisis on the continent. While SSA accounts for only one-tenth of the global population, it bears the brunt of the disease, with more than 80% of AIDS-related deaths worldwide.



Source: UNAIDS, 1999

Current statistics indicate that two decades since the epidemic surfaced, sufficient actions have not been taken to mitigate the spread of the disease. The result is millions of new infections and unnecessary suffering and death. In 1999 alone, it was estimated that out of the 5.6 million newly infected adults and children, 3.8 million were found to be in SSA.

Estimated number of adults and children newly infected with HIV during 1999



Source: AIDS epidemic update: December 1999 (UNAIDS)

3-7 December 2000, Addis Ababa, Ethiopia

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For questions regarding this web site contact the

Last updated: September 07, 2000 11:37.

INTERNATIONAL

No treatment:
AIDS patient

No Money, No Meds

South Africa needs access to cheap AIDS medicine, but drug companies want a say in what they get and how they get it. Now Al Gore is caught in the cross-fire.

BY MARCUS MABRY

VERONICA MINGOMA, A 35-YEAR-old mother of three, was diagnosed with AIDS more than a year ago. But doctors at Rietvlei Hospital, in South Africa's impoverished Eastern Cape province, didn't do anything about it. They didn't even tell Mingoma there are treatments that could prolong her life. Why not? On the \$33 a week Mingoma earned working in a furniture factory, she couldn't pay for AIDS drugs anyway. "If we told [her] there was treatment but you can't af-

ford it, that would be cruel," says Rietvlei Supt. Nigel Hoffman. Now Mingoma's bony limbs are covered in scales, and she has trouble walking. Talking is a chore. She opens her mouth, filled with yellow sores, and fights to tell a reporter, "I worry about my children."

Is it right to put a price tag on survival? South Africa's government thinks not. It wants to bypass Western pharmaceutical firms and produce AIDS drugs on its own, or to import them at the cheapest possible cost—perhaps from so-called patent-pirate countries. That, in turn, has whipped up

emotions in Washington, where trade officials and corporate lobbyists are determined to protect intellectual-property rights. AIDS activists have taken up the South African cause: protesters from ACT UP, the confrontational AIDS lobby group, are now dogging the campaign of Al Gore, casting him as the leading villain in the dispute.

This is not a narrow bilateral issue, nor is it a simple one. Ninety percent of the world's 33 million HIV/AIDS cases are in Africa, Latin America and Asia. The vast majority of infected people in those areas

A Disease Unchecked

Here are estimated numbers of AIDS deaths and existing cases worldwide by region.



	HIV/AIDS deaths*	Living with HIV/AIDS**
① Sub-Saharan Africa	13.7 million	23.3 million
② South & Southeast Asia	1.1 million	6 million
③ Latin America	520,000	1.3 million
④ North America	450,000	920,000
⑤ Western Europe	210,000	520,000
⑥ Caribbean	160,000	360,000
⑦ North Africa & Middle East	70,000	220,000
⑧ East Asia & Pacific	40,000	530,000
⑨ Eastern Europe & Central Asia	17,000	360,000
⑩ Australia & New Zealand	8,000	12,000
Total	18.3 million	23.6 million

*Estimated adult and child deaths because of HIV/AIDS from start of epidemic to end of 1998.
 **Adults and children estimated to be living with HIV/AIDS as of the end of 1998

Source: UNAIDS

ROB HERNANDEZ / Los Angeles Times

AIDS

Continued from A1

said Dr. Peter Piot, executive director of the UNAIDS program, at a London news conference Tuesday. "The crisis is actually growing."

Dr. Roger Detels, an epidemiologist at UCLA, said: "The bottom line is, we need to be very concerned about the AIDS/HIV epidemic, despite the significant advances that have been made in treatment. The epidemic is continuing and, in some countries, continuing at a very high rate indeed."

The tragedy, said Dr. Thomas Coates, head of the UC San Francisco AIDS Research Institute, "is that we know how to stop the epidemic but are just not willing to pay for it." If developed countries spent only \$2.5 billion on such an effort in developing countries, he said, "we could cut the infection rate in half."

The money would be spent on condoms, marketing of condoms, treatment of other sexually transmitted diseases (which increase susceptibility to HIV), the use of antiviral agents during childbirth to prevent spread from mothers to children, testing of the blood supply, needle exchange programs and drug abuse treatment.

According to the new report, 5.6 million people will have been infected with the AIDS virus this year.

The spread of the disease has severe economic as well as personal

Please see AIDS, A27

LOS ANGELES TIMES

Nov. 24, 1999 Sat.

AIDS

Continued from A26

consequences. According to a survey of commercial farms in Kenya, for example, illness and death have replaced retirement as the most common reasons for employees leaving their jobs. At one Kenyan sugar estate cited by the U.N. report, company spending on funerals increased fivefold between 1989 and 1998, and health care expenditures increased tenfold.

The steepest HIV growth curve, the report said, is in the former Soviet Union, where infection is the inevitable byproduct of startling rates of intravenous drug abuse. In the Russian Federation, nearly half all cases of HIV infection reported since the start of the epidemic occurred in the first nine

Many of the infections were seen in large cities such as Moscow, but even remote regions are feeling the impact. In the Siberian city of Irkutsk, nearly 1,300 infections have been reported, most of them this year.

Drug abuse-related infections are also a growing problem in the Middle East. For instance, drug use is responsible for two-thirds of recorded cases of HIV infection in Bahrain, half of the cases in Iran and one-third of those in Tunisia. Although the actual number of cases is still small in those areas, U.N. officials expect the figures to grow dramatically because of other evidence that high-risk sexual practices are common.

Even in developed countries, the news is not all good. Despite the outlay of \$3 billion a year in the United States for HIV therapy, the

dropping, indicating that there is a limit to the effectiveness of existing treatments.

Furthermore, some studies have suggested that the lowering of the death rate has led to a resurgence of risky sexual behavior among a population that has begun to view HIV infection as a controllable problem more like diabetes than cancer.

About 17,000 people died of AIDS in the United States last year, down from 50,000 two years ago. But 40,000 people developed new HIV infections.

There were some suggestions of good news in the report, however.

Some countries in Latin America have joined the ranks of those providing expensive antiviral drugs—including the new protease inhibitors—to the HIV-positive. Brazil, for example, spent about

drugs for about 75,000 people.

Brazilian authorities say they got at least \$136 million of that back in savings on hospitalization treatment for people with full-blown AIDS.

Argentina has also been providing antiviral drugs, leading to a 40% drop in the number of AIDS cases in the last two years. But not all countries can afford this. Guatemala, for example, provides drugs to just 185 people out of the more than 50,000 in the country who are HIV-positive.

Thailand's well-established HIV prevention efforts are also bearing fruit. A study of pregnant women in the high-risk northern Thai province of Chiang Rai showed that the proportion who were HIV-positive fell from a peak of 6.4% in 1994 to 4.6% in 1997. The greatest reductions were seen in women under the

Los Angeles Times
California USA

Nov. 24, 1999 Wed.

DAILY 28¢

DESIGNATED AREAS HIGHER

AIDS Death Toll at New High Despite Advances

■ **Health:** Drug treatments gain in the U.S. and Europe, but cases are rising rapidly in the developing world. Deaths for 1999 will reach 2.6 million, according to U.N. study. Africa is hardest hit, while infections soar in the former Soviet Union.

By THOMAS H. MAUGH II
TIMES MEDICAL WRITER

As the world closes in on a new millennium, the AIDS conflagration continues to blaze out of control throughout most of the developing world.

Despite lowered death rates in the United States and Europe as a result of new drug therapies, more than 50 million people worldwide will have been infected by the AIDS virus and 16.3 million will have died by the end of the year, according to a report issued Tuesday by a United Nations program on HIV and AIDS. In 1999 alone, there will have been 2.6 million fatalities—the highest yearly total since the epidemic began two decades ago.

More than 70% of the HIV-positive live in sub-Saharan Africa, a region that contains only 10% of the world's population. U.N. officials predict that life expectancy at birth in the region, which climbed from 44 in the early 1950s to 59 early this decade, will drop back to 45 sometime in the next five to 10 years.

The most glaring current hot spot, however, encompasses the former Soviet Union, where the proportion of the population living with HIV has doubled in only two years.

Women are increasingly bearing the brunt of the disease, according to the report. In sub-Saharan Africa, there are now HIV-positive women for every five such men—the first time infected females have clearly outnumbered males anywhere in the world. Among teenagers in the region, HIV-positive girls outnumber boys by five or six to one. More than 11 million children have lost their mothers to the disease.

Tragically, more than half the victims worldwide are under the age of 25, and few will live to see their 35th birthdays.

"The epidemic is far from over,"

Nov. 24/99 Please see AIDS, A28

U.N. and World Bank Unite To Wage War on Malaria

By BARBARA CROSSETTE

getting governments to focus on malaria," said James D. Wolfensohn, president of the World Bank, at today's news conference. "We are trying to make the case to financial institutions that this is central to the economic development of Africa."

James Gustave Speth, administrator of the United Nations Development Program, said his agency was well placed to look at the environmental situation in countries struck by malaria — issues of sanitation, for example. He said the "social fallout" of malaria was also of concern to his agency.

Carol Bellamy, executive director of Unicef, the United Nations children's fund, said her organization would focus, as it already does, on local-level work in poor communities, where malaria contributes significantly to a high maternal mortality rate and to a high incidence of anemia among women and children.

Dr. Nabarro, now strategic director for human development at Britain's Department for International Development, said in an interview today that "collective brainpower" was necessary if health officials had any hope of even halving malaria

deaths in a decade. He said wiping out malaria in the near future would be virtually impossible.

Dr. Nabarro, who has worked in Iraq and Nepal as well as Africa, and taught international community health at the Liverpool School of Medicine, explained that the project did not have a single goal, like some public health campaigns. "What we're instead trying to do is approach an incredibly complicated health issue that's associated partly with the way in which people have to live, partly with a parasite that has one of the best disguises that we know — in the face of any threat it can change its coat — and an insect vector that seems to be able to shake off insecticides almost as quickly as we produce them."

Dr. Tore Godal of Norway, a tropical medicine expert who is now acting director of the anti-malaria program, said in an interview that one of the best hopes of finding medicine to cure the disease may be in a plant cultivated in China and used there and in Vietnam as a very effective treatment.

The plant is the ching hao or "The Chinese have used it for more than 2,000 years against fevers," Dr. Godal said.

The World Health Organization has been encouraging China to make medicines from the plant to standards that would meet international requirements, Dr. Godal said. He said that the compound in ching hao attacks malaria so quickly and at so many levels that it also seems to help curtail the spread of the disease by destroying parasites before they can be passed on.

Dr. Godal has also been involved in trying to persuade pharmaceutical companies to invest in anti-malarial drugs. He said only one, Smith Kline Beecham, has showed much interest.

"The Vietnamese war actually made the U.S. Army invest big in malaria drug development, and so some pharmaceutical companies took up leads from that effort," he said. But today, he said, "There is no sufficient commercial market for the drugs," so pharmaceutical companies don't see enough potential for profit.

A killer of the poor still stalks Africa and parts of Asia and Latin America.

Philippine Daily Anglian
Malaria kills millions annually *April 24/99*

NAIROBI, Kenya—Officials from 12 African countries gathered in Nairobi today as part of the World Health Organization's campaign to control malaria.

The WHO initiative aims to coordinate efforts to fight the disease throughout Africa. The continent accounts for 90 percent of the world's malaria cases, the organization said.

"Malaria is not only a health problem in Africa. It has everything to do with our development," said Edwin Afari, a WHO official at the meeting.

The direct and indirect costs of malaria rose to an estimated \$2 billion in 1997 from \$800 million in 1987, said Dr. Rufaro Chatora, the WHO's representative to Kenya.

Malaria kills an estimated 1.5 to 2.7 million people annually.

"They die because they lack access to health care, life-saving drugs and treated bednets," Chatora said. *AP*

Los Angeles Times USA
May 21, 2000 SUN
WHO Targets AIDS, Smoking, Malaria

GENEVA—The World Health Organization called Saturday for more concerted international action against AIDS, malaria and smoking-related diseases, while also raising concerns about cloning.

Closing its annual conference, the WHO presented a long list of action needed to fight the most formidable health problems, including HIV, the virus that has infected about 34 million people worldwide and threatens to reverse social and economic developments in Africa.

The 191-nation assembly said more must be done to improve access to drugs to treat AIDS and related illnesses in developing countries.

The assembly also urged governments to introduce more measures such as healthy eating programs and tobacco taxation. And delegates discussed plans for the WHO to become more active on issues such as human cloning.

—Associated Press

IN THIS ISSUE

VOLUME 270, NUMBER 20

2 LETTERS

EDITORIALS & COMMENT

3 OF AIDS & MISSILES

4 ANTITRUST & THE MEDIA—I
*Robert W. McChesney*5 ANTITRUST & THE MEDIA—II
*Robert H. Lande*6 ISRAEL'S LEBANON CLIENTS
*Neve Gordon*7 CORPORATIONS REIMAGINED
Michael Lerner

7 IN FACT...

COLUMNS

6 MY ADVICE FOR THE FINAL
ENRAGED CUBAN-AMERICAN
DEMONSTRATOR IN MIAMI
*Calvin Trillin*8 BEAT THE DEVIL
He Should Remember His Sister
*Alexander Cockburn*9 DIARY OF A MAD LAW PROFESSOR
Field of Daydreams
*Patricia J. Williams*10 FULL-COURT PRESS
Back to the Forward
Eric Alterman

ARTICLES

11 GORE'S OIL MONEY
What's good for Occidental is bad for
Colombia's U'was.
*Ken Silverstein*15 THE DETAILS OF LIFE
All children need more than test-taking
skills. Pet burials, for instance.
*Jonathan Kozol*20 COPYRIGHT AS CENSORSHIP
In an effort to keep its secrets, Westminster
is using an astonishing approach.
*Jon Wiener*22 FOX NIXES ZINN FLICK
A radical retelling of US history has
proved a tough sell in Hollywood.
David Corn

BOOKS & THE ARTS

25 O'SHAUGHNESSY: Pinochet: The
Politics of Torture
CULLATHER: Secret History: The CIA's
Classified Account of Its Operations in
Guatemala, 1952-1954
*Greg Grandin*28 SPECTOR: Prague Territories: National
Conflict and Cultural Innovation in
Franz Kafka's *Fin de Siècle*
ROBERTSON: The 'Jewish Question'
in German Literature, 1749-1939:
Emancipation and Its Discontents
*Paul Reitter*31 MUSIC
Herbie Hancock
*Gene Santoro*34 FILMS
Gladiator
*Stuart Klawans**Cover design by Scott Stowell/Open,
photo by AP/Wide World;
illustrations by Karen Caldicott*

EDITORIALS

Of AIDS and Missiles

In the post-cold war world, there *are* threats to national security. The trick is distinguishing the real from the manufactured ones and deciding how to counter them. The past weeks have offered an edifying demonstration of how the national security class handles the important task of threat assessment. The Clinton Administration has designated AIDS a danger to US national security, noting that the rapid spread of the killer disease abroad—especially in Africa—could destabilize nations, spark ethnic warfare and prevent the growth of free-market democracies. A National Intelligence Estimate projected that one out of four people in southern Africa will likely die from AIDS and that other regions—southern Asia and parts of the former Soviet Union—might suffer a similar “demographic catastrophe.” The White House move was commendable, a refreshing change from the Al Gore-led effort to bully South Africa into overturning laws, opposed by the pharmaceutical companies, that would make AIDS drugs cheaper.

But although the Administration was willing to expand national security interests beyond the traditional military and economic concerns, it has been reluctant to battle the threatmongers on the right who proclaim that the United States is menaced by a nuclear missile attack from “rogue nations”—most notably, North Korea, Iran and Iraq—and who assert that the Pentagon must build a national missile defense system (a lesser Star Wars) to thwart this danger. President Clinton will decide this fall whether to go ahead with a limited system. Gore has blasted George W. Bush for

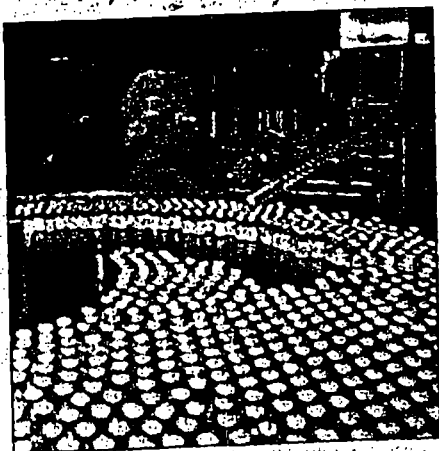
supporting an extensive antimissile program but supports a limited shield. That support reinforces the argument that a threat does exist and must be countered by missiles that can hit other missiles.

The threat of AIDS overseas is more real than, say, North Korean missiles. The Administration is considering removing North Korea from its terrorism list, and it has offered to end economic sanctions if Pyongyang eliminates its ballistic missile and nuclear weapons programs—an initiative that ought to be tried before rushing to build an antimissile defense system. As for the other rogues, Iran has taken tentative steps toward democracy, and Iraq's ability to develop new missiles is hindered by international sanctions.

The difference in the resources to be applied to these two threats is staggering. Regarding overseas AIDS, the Administration has doubled its budget request—increasing it to \$254 million. That's less than one-tenth of 1 percent of the US military budget. The United States has already spent more than \$120 billion on missile defense weapons without deploying an effective system. The current Clinton budget calls for \$12.7 billion in missile defense spending over the next five years. The Pentagon estimates that the first stage of a system will cost \$26 billion; the Congressional Budget Office says the real cost might be \$60 billion.

Although it is difficult to estimate the cost of combating AIDS in Africa—much of the health infrastructure there would have to be expanded or bolstered to implement an effective anti-AIDS campaign—the Joint United Nations Program on HIV/AIDS says that about \$1 billion to \$3 billion would adequately fund prevention programs, and a similar amount would take care of treatment programs.

Sept 18, 2000, Mon



Health officials hope production snags don't lead to a shortage of flu vaccines.

Makers of Flu Vaccine Are Behind Schedule

Immunizations • Delay results from difficulty in producing inoculations against the season's new strains.

By JANE E. ALLEN
TIMES HEALTH WRITER

If you're the type who likes to get a flu shot early in the fall, take note. Most people are going to have to wait until November to get the vaccine.

Vaccination campaigns that normally begin in October have been pushed back a month because of difficulties producing vaccines against new flu strains. Health officials, meanwhile, are hoping a shortage doesn't develop.

With the four manufacturers of U.S. flu vaccines about a month behind their typical delivery schedule, doctors have been advised to first vaccinate the highest-risk patients—the elderly, those 50 to 64 with chronic diseases and pregnant women—and health care workers. These groups will be vaccinated as soon as supplies become available; mass vaccination of healthier Americans should follow.

Each year, scientists at the World Health Organization and federal Centers for Dis-

Please see Influenza, S3

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Los Angeles Times
Continued from S1 9-18-2000

ease Control and Prevention in Atlanta predict which strains are the likeliest to create a problem in the coming year. In the last two years, they targeted A/Sydney and A/Beijing strains as well as a B strain. But for the 2000-2001 season, infectious disease experts determined that two new A strains were likely to be troublesome: Type A/Panama and A/New Caledonia, along with B/Yamanashi, a carry-over from last year.

This year's production delays stem from problems encountered by the four companies that supply the U.S. with vaccines, which are made from inactivated flu viruses.

Although they use slightly different technology, all had trouble generating enough of the A/Panama component of the vaccine, which was only identified in late April as a new target.

Aventis Pasteur, which supplies more than half the U.S. flu vaccine supply, normally begins shipping its vaccine in late July or early August. It has been in round-the-clock production "putting the pedal to the medal" and sent out its first shipments the first week of September, said spokesman Len Lavenda.

Further stalling this year's production were quality control violations and other manufacturing issues that Parkdale Pharmaceuticals Inc. and Wyeth-Ayerst Laboratories Inc. have been working with the FDA to clear up. Medeva Pharma Ltd., a British company, is the fourth U.S. supplier.

Beyond the delays, "we don't know how much vaccine will get to the marketplace," Lavenda said. Charlis Thompson, a CDC spokeswoman, predicted that there should be some indication about the supply by the end of September.

Typically, public health officials conduct immunization campaigns in October and early November. That gives them time before the arrival of the winter flu season, which usually begins in December and continues through March.

To avoid having patients show up at clinics and offices only to find out vaccine supplies have dried up, the CDC advised that health-care providers, health organizations and other groups planning mass vaccination campaigns for the 2000-2001 season postpone those programs until November.

"We feel confident that even receiving the vaccine in November or getting the vaccine throughout the season while the virus is circulating is going to be of tremendous

public benefit," Thompson said.

No one knows how closely this year's delayed vaccination campaigns will bump up against outbreaks of the illness, but last year, flu activity began to increase in mid-December and peaked during the weeks ending Dec. 25 and Jan. 15, 2000, CDC surveillance data show. Widespread flu was first reported the week of Dec. 18.

It typically takes about two weeks after vaccination for a person's body to develop enough antibodies to protect against an assault by the virus, but maximum immunity is reached at about four weeks, said Dr. Robert Fick, a pulmonary specialist who teaches at Stanford University. Because flu cases often peak in February, vaccination in November or later still can be valuable.

The CDC earlier this year recommended that people 50 to 64, not just those 65 and over, be vaccinated. In light of the production logjam, it has advised doctors to make contingency plans in case of shortfalls by first vaccinating the elderly, those who live in nursing homes and those 50 to 64 who suffer from heart, lung or kidney problems, diabetes or severe anemia, because they're particularly vulnerable to potentially life-threatening flu complications. Anyone with an immune disorder or any woman in the second or third trimester of pregnancy also should be a priority, CDC said.

Natalie Smith, the immunization branch chief for the state health department, also said that the strategy of vaccinating those at high risk first should work. "Maybe the healthy younger folks can wait a little bit," she said.

In all, as many as 76 million people are at high risk for serious

Los Angeles Times Sept 18, 2000
MCN

complications from the flu, which commonly leads to 20,000 deaths and more than 110,000 hospitalizations each year.

The flu infects the respiratory tract and can cause high fever and major complications including pneumonia, which can be deadly.

Flu spreads through the air from sneezing and coughing or through close physical contact.

"Vaccination against the flu is the best defense against complications of the flu, which are quite substantial," said Dr. Norman H. Edelman, a scientific affairs consultant to the American Lung Assn., and medical school dean at the State University of New York at Stony Brook.

However, he said, physicians will have to decide whether or not

to use any of the four prescription drugs that may ease the illness.

Two of the drugs, zanamivir and oseltamivir, marketed as Relenza and Tamiflu, respectively, were rolled out last year. They belong to a class of drugs called neuraminidase inhibitors and can reduce the severity and duration of flu infections with A and B strains.

There are two antiviral medications effective against Type A flu strains, amantadine and rimantadine, which are FDA-approved for treating and preventing influenza A. However, because both drugs can produce neurological and other side effects, they're not recommended for widespread use except in the case of potentially devastating outbreaks.

Blackmailers Use VENOM

Essen, Germany- Unknown blackmailers have threatened to lace food in stores across Europe with snake venom unless they are given a fortune in diamonds, according to a prosecutor. Law officials recently invited top managers from 60 European companies to an urgent meeting in Essen to discuss the threat, Essen prosecutor Norbert Golsong said Monday. Golsong said threats began in January and were made public only now to avoid hampering the investigation. The blackmailers have been sending computer disks to European food companies. The disks contain a threat to inject food with venom from cobras, mambas and other snakes if the companies fail to give them 400 million marks (\$266 million) in diamond, the newspaper said. AP

Source: Philippine Daily Inquirer (Philippines)
April 17, 1996 Wed. pp. 16

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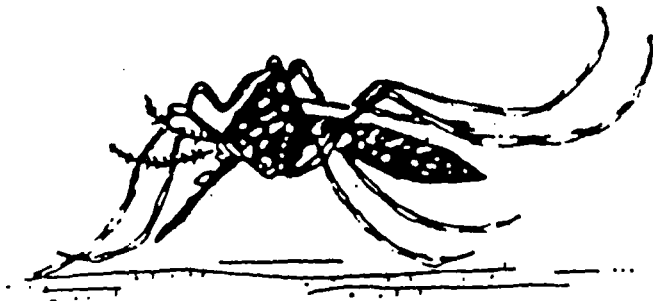
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ESSEN, Germany - Cybercriminals have threatened to "open up" Europe with strikes against banks they are given a fortune in diamonds, according to a newspaper. The criminals recently invited top managers from 10 leading companies to an urgent meeting in order to discuss the threat. Even the British Secret Service said Monday. German and French began in January and were made public only now to avoid panic, said the investigation. The blackmailers have been sending computer disks to European steel companies. The disks contain a threat to infect firms with vermin from cobras, marabhas and other snakes if the companies fail to give them 400 million marks (\$266 million) in diamonds, the newspaper said.

Di, Fergie aren't invited!

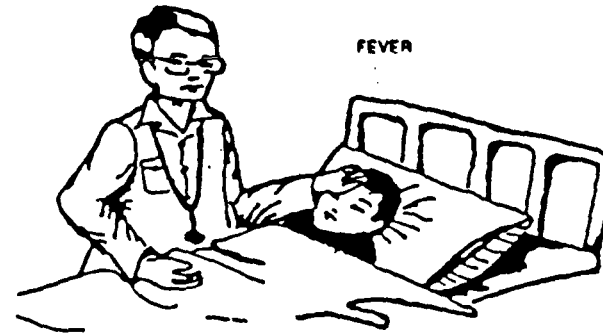
WHAT IS DENGUE H-FEVER?

Dengue Hemorrhagic Fever (DHF) is an acute infectious viral disease usually affecting infants and young children. It is characterized by fever during the initial phase, and other symptoms like headache, pain in the eye, joint pain, muscle pain, etc. followed by signs of bleeding, e.g., *petechiae* (red tiny spots on the skin), nosebleeding, gumbleeding. If there is blood in the stools and/or blood in the vomitus and accompanied by shock, this is called Dengue Shock Syndrome and is often fatal.



Aedes aegypti, the transmitter of the disease, is a day-biting mosquito which lays eggs in clear water container, such as flower vases, cans, rain barrels, old rubber tires, etc. The adult mosquitoes rest in dark places of the house.

WHAT ARE THE SYMPTOMS OF DENGUE H-FEVER?



1. Sudden onset of high fever which may last 2 to 7 days.
2. Joint & muscle pain and pain behind the eyes.
3. Weakness
4. Skin rashes — *maculopapular* rash or red tiny spots on the skin called *petechiae*
5. Nosebleeding when fever starts to subside
6. Enlargement of liver
7. Vomitting of coffee-colored matter
8. Dark-colored stools



MEDICINE DIGEST

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International Lead Articles

Dengue fever

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Dengue fever

Jit Singh

Dr Singh is a Public Health Consultant who is Executive Director, Grewal Healthcare Sdn Bhd, Kuala Lumpur, Malaysia.

Hundreds of thousands of dengue cases are reported worldwide each year. Given the difficulty in obtaining full reporting, the actual number of human infections is probably much higher than the number reported. Dengue is usually a nonspecific febrile illness that resolves with supportive therapy but the clinical spectrum ranges from asymptomatic infection through severe haemorrhage and sudden fatal shock. The pathophysiology of the severe forms of dengue may be related to sequential infection with different serotypes, variations in virus virulence, interaction of the virus with environmental and host factors or a combination of these factors. Control of dengue at the present time is dependent on control of the principal vector mosquito, *Aedes aegypti*. Efforts to achieve such control are now focusing on community education and action towards eliminating this mosquito's breeding sites near human dwellings. Vaccine development continues, but at present the only way to avoid dengue in an area where it is endemic or epidemic is to use repellents and mosquito barriers. The movement of people to and from tropical areas makes dengue an important differential diagnosis in any patient with an acute illness and

history of recent travel to tropical areas.

Dengue fever is an acute febrile infectious disease, caused by the dengue virus from genus *Flavivirus*.¹ It is the most prevalent flavivirus infection of humans, with a worldwide distribution in the tropics and warm areas of the temperate zone corresponding to that of the principal vector, *A. aegypti*. There are four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), and all are currently circulating in the Pacific Islands, Americas, Asia, and Africa. When simultaneous or sequential introduction of two or more serotypes occurs in the same area, there may be an increased number of cases with worse clinical presentation (dengue haemorrhagic fever). The term 'haemorrhagic' is imprecise, because what characterizes this form of the disease is not the presence of haemorrhagic manifestations, but the abrupt increase of capillary permeability, with diffuse capillary leakage of plasma, haemo-concentration and, in some cases, with non-haemorrhagic hypovolaemic shock (dengue shock syndrome).

Epidemiology

The highest incidence of dengue is in southeast Asia, India and the American tropics, where *A. aegypti* can be found all the year around. Movement of human populations by fast transport has helped in the rapid spread of dengue fever to the West Indies and the Americas. In the 1980s, dengue emerged in explosive epidemics in Brazil, Cuba and Mexico. In areas such as South and South

EDITOR

Paul Chinnock, MSc, MIBiol, DLSh&TM

ASSISTANT EDITOR

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INTERNATIONAL SALES OFFICE

11-12 Bouverie Street Tel: 44-171-353 0585

London EC4Y 8DP, UK Fax: 44-171-353 0614

Web site: <http://www.hello.co.uk/medigest/>email (editor): paul@tsg.co.uk

Philippines Entered as second class mail at Makati Central Post Office under permit number 604 dated May 29, 1995.

For reprint information in North America, contact: International Reprint Corporation, 968 Admiral Callaghan, #268, PO Box 12004, Vallejo, CA 94590, USA

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All subscription enquiries & correspondence

Medicine Digest

135 Cecil Street

Tel: 65-223 3788

#13-00, LKN Building

Fax: 65-226 0634

SINGAPORE 069536

65-221 4788

or to your nearest Medicine Digest office

Printed in Hong Kong

Enquiries & Correspondence**Hong Kong and China**

Mary Ng, Tony Choi

Rm 2102 Tung Sun Commercial Centre

194-200 Lockhart Rd

Tel: 852-2519 9303

HONG KONG

Fax: 852-2507 3817

Email: mimsasia@netvigator.com**Indonesia**

Sylvia Djajamiharsa, Lili Sopannata

Jl Sutan Iskandar Muda No. 18J

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Tel: 62-21-725 1255

Jakarta 12240,

62-21-725 1252

INDONESIA

Fax: 62-21-725 2119

Email: mimsindo@indosat.net.id**Malaysia**

Shiamala Govindasamy, MG Menon

Suite 5-03, 5th Floor, BICMA Building

Lot 2, Jin 243/51A, 46100 Petaling Jaya

Selangor,

Tel: 03-776 1615

MALAYSIA

Fax: 03-776 1418

Email: medi@medimed.po.my**Pakistan**

Azhar Iqbal

Medical Publications Pakistan Pvt Ltd

F/4 RSM Square E/1, Block 7/8

Central Commercial Area

Shaheed-e-Millat Road

Tel: 92-21-4530696-7

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Fax: 92-21-454 5895

Philippines

Joy G del Rosario, Jun F Perez

2/F Kalaw-Ledesma Condominium

117 Gamboa St.

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Tel: 63-2-815 1687

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PHILIPPINES

Email: medicinedigest@medimedia.com.ph**Singapore**

Florence Lo-Kiang, MG Menon

135 Cecil Street

Tel: 65-223 3788

#13-00, LKN Building

Fax: 65-226 0634

SINGAPORE 069536

65-221 4788

Email: medimedia@mimsmmi.com.sg**Taiwan**

Lisa Lin

No. 11, Lane 130, Sec. 4,

Tel: 886-2-86633101

Hsin Hai Road

886-2-86633102

Taipei, TAIWAN, R.O.C.

Fax: 886-2-86633103

Email: twims@ms6.ninet.net**Thailand**

P. Nonglak

368 Sukumvit 68 Bangna

Tel: 66-2-398 6273

Bangkok 10260, THAILAND

Fax: 66-2-398 6240

Email: nuntavd@mzart.inet.co.th**MediMedia Asia Pte Ltd**

Vietnam Representative Office

Room F7, 2 Phung Khac Khoan Street

Dakao Ward, District 1

Tel: 848-829 7923

Ho Chi Minh City, VIETNAM

Fax: 848-822 1765

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East Asia, where all four dengue virus types are hyperendemic, children are almost exclusively affected, and seroprevalence approaches 100% by young adulthood.

Occurrence of a dengue epidemic requires the presence of i) the virus, ii) the vector mosquito (*A aegypti*), and iii) a sufficient number of susceptible human hosts. Outbreaks may be explosive or progressive, depending on the density and susceptibility of the vector, the strain of dengue virus, and the degree of exposure occurring between humans and vectors.

Transmission occurs by the bite of *A aegypti* female mosquitoes – the same vector of urban yellow fever – a day-active species with low fly-autonomy that is abundant in and around human habitations. In many countries *Aedes albopictus* may also be responsible for transmission. Viraemic humans (till the fifth day of disease) serve as the source of virus for mosquito infection; there is no person-to-person transmission. Movement of viraemic humans provides the principal means of spread, and rapid air travel is a factor in most recent epidemic emergencies.²

Although homotypic immunity is complete and lifelong, cross-protection between virus types is incomplete and transient. There is a strong association between reinfection by another serotype and the occurrence of dengue haemorrhagic fever (DHF), due to immunopathological processes, such as immune enhancement and immune clearance.³ Outbreaks usually occur in summer, when ambiental conditions are ideal for vector proliferation.

Clinical manifestation

Since the recognition of DHF in the 1950s investigators have sought to define the clinical differences between severe and mild forms of dengue (see Figure 1). Mild haemorrhagic manifestations, such as epistaxis, petechiae, gingival bleeding and menorrhagia, are accepted as part of the clinical picture of classic dengue. Manifestations of severe dengue include severe haemorrhage leading to shock through blood loss, sudden increased vascular permeability leading to shock with or without haemorrhage and severe encephalopathy with hepatitis. The classification of severe dengue has been complicated by the variety of these clinical pictures, for which the underlying pathophysiology may be different.

Symptoms begin about 2 to 15 days after the bite of an infective mosquito, when the patient typically suffers sudden onset of headache, fever, retroorbital pain, backache, bone and joint pain, weakness, depression and malaise. Some patients have an evanescent rash over the thorax and joint flexures. There may be flushing of the face and conjunctivitis as well as taste aberrations, anorexia, nausea, vomiting and abdominal pain. Lymphadenopathy and hepatomegaly may occur but splenomegaly is infrequent. Patients may complain of sore throat, cough, groin pain, hyperesthesia, dizziness, photophobia, eye pain and, rarely, a 'yellow flamelike' colour to objects.

Fever and associated symptoms may subside after 3 or 4 days and the patient may recover completely. Alternatively the decline in fever may be followed 1 to 3 days later by a resurgence of fever and symptoms,

giving a 'saddleback' appearance to the temperature curve. A second rash, varying in form from scarlatiniform and maculopapular to petechial and occasionally purpuric, may appear with the initial decline of the fever. Severe itching, especially of the hands and feet, may accompany this rash, which is sometimes followed by desquamation. The symptoms persist for 1 to 3 days more and then subside with the fever.⁴

During the course of the illness there is often a relative or paradoxical bradycardia in the face of increased temperature. Patients may have haemorrhagic manifestations such as epistaxis or menorrhagia. Jaundice is rare. Convulsions may occur with the onset of fever. The spinal fluid is almost always clear with no elevation of cell count but the pressure may be increased. Depression, weakness and blurred vision may resolve slowly during convalescence. Patients may take several weeks to recover completely.

Although these symptoms characterize 'classical' dengue fever, dengue virus infection may also manifest as a nonspecific febrile illness which can be confused with influenza, measles or any nonspecific vital syndrome. The lack of a clear clinical pattern for dengue makes laboratory diagnosis a necessary part of any definitive evaluation of the disease.

Patients who develop DHF or other severe manifestations of dengue generally have an onset of illness similar to that seen in 'classical' or nonhaemorrhagic dengue. The course usually begins with the sudden onset of fever, headache, nausea, vomiting, abdominal pain, pharyngitis, lymphadenopathy and sometimes a rash, which may be petechial or even

ecchymotic early in the course.

The liver may become enlarged and pleural effusions may develop, usually beginning on the right side. As the fever begins to drop around Day 3 to 5, circulatory instability may develop with signs of decreased peripheral perfusion. Profound shock may follow. Disseminated intravascular coagulation and severe gastrointestinal haemorrhage have been described.

The descriptions of such patients led to the following WHO case definitions for DHF: (1) fever; (2) haemorrhagic manifestations, including at least a positive tourniquet test (except in shock cases), and either major or minor bleeding phenomena; (3) thrombocytopenia (platelet count less than or equal to 100 000/mm³); and (4) haemoconcentration (haematocrit increased by 20% or more relative to baseline values, or objective evidence of increased capillary permeability).

Significant thrombocytopenia may occur in both DHF and 'classical' dengue. A fall in platelet count associated with a rising haematocrit may suggest the development of DHF.⁵

Diffuse capillary leakage of plasma is responsible for the haemoconcentration. In the presence of haemoconcentration and thrombocytopenia, the patient is considered to be seized by dengue haemorrhagic fever and classified according to the following classification produced by WHO:

Grade I – thrombocytopenia + haemoconcentration. Absence of spontaneous bleeding.

Grade II – thrombocytopenia + haemoconcentration. Presence of spontaneous bleeding.

Grade III – thrombocytopenia +

haemoconcentration, haemodynamic instability: filiform pulse, narrowing of the pulse pressure (<20 mmHg), cold extremities, mental confusion.

Grade IV - thrombocytopenia + haemoconcentration. Declared shock, patient pulseless and with arterial blood pressure = 0 mmHg (dengue shock syndrome - DSS).

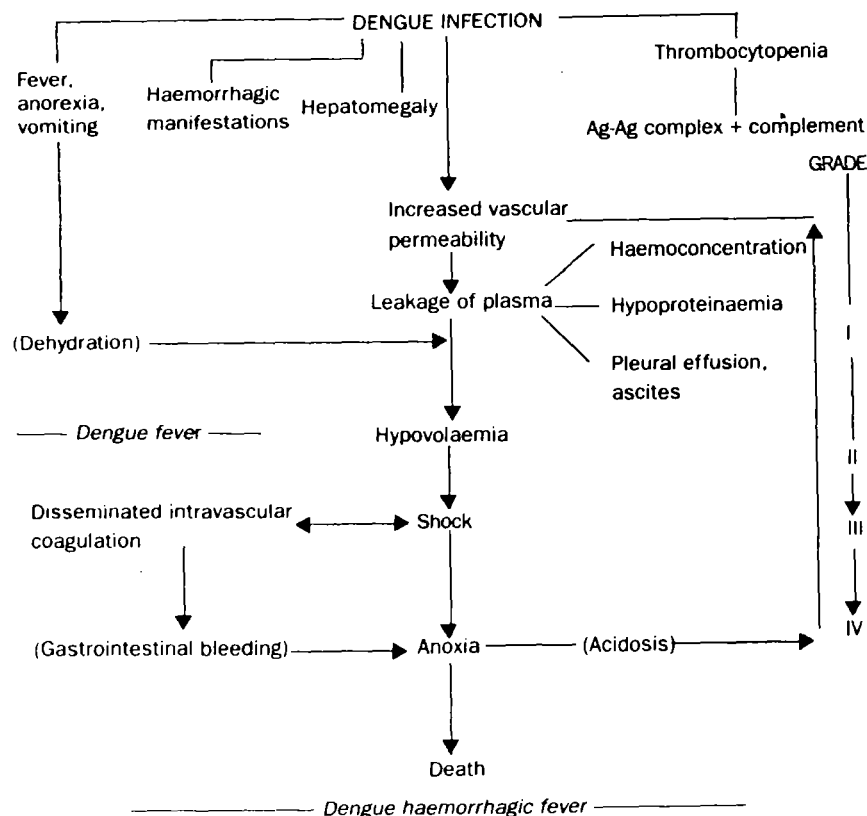
The case-fatality of DHF/DSS is

10% or higher if untreated. With supportive treatment, less than 1% of such cases succumb. Recovery is rapid and without sequelae.

Diagnosis

Classical dengue fever may be confused with a variety of febrile illnesses, including influenza, measles, typhoid fever and malaria.

Figure 1 Pathophysiology and Disease Severity of Dengue Infection
(Suchitra Nimmannitya and M J Cardoso)



DHF may be confused with sepsis, toxic shock and any of the viral haemorrhagic fevers including yellow fever. Diseases with specific treatments, such as bacterial meningitis, sepsis, malaria and Lassa fever, should be ruled out.

Although the aetiological diagnosis of dengue is extremely important and desirable in terms of Public Health Care, it is absolutely unnecessary for the early institution of supportive therapy. Dengue is always a diagnosis of exclusion, and other diseases with the same initial clinical presentation must be suspected. In order to help the clinician in the detection of severe forms of dengue (DHF/DSS), even when the definitive diagnosis has not been made yet, there are three essential laboratory tests that may help in the evaluation of the real clinical conditions of the patient and its early supportive management: total white blood cells count, total platelets count and micro-haematocrit.

- Total white blood cell count: In case of dengue, this test will reveal leukopenia. The presence of leukocytosis and neutrophilia excludes the possibility of dengue and therefore bacterial infections (leptospirosis, meningococcal meningitis, septicemia, etc.) must be considered.
- Thrombocytopenia (<100 000/mm³): Total platelets count must be obtained in every patient with symptoms suggestive of dengue for three or more days of presentation. Leptospirosis, measles, rubella, meningococcal meningitis and septicemia may also cause thrombocytopenia.
- Haematocrit (micro-haematocrit): According to the definition of DHF, presence of haemoconcentration

(haematocrit elevated by 20%) is necessary.

Specific diagnosis of dengue infection is made by isolating the virus from the patient's blood. Acute serum samples are inoculated into tissue cultures of mosquito cells or directly into live *Toxorhynchites* or *Aedes* mosquitoes. Isolates can be identified from 2 to 7 days after inoculation depending on the actual technique used. Viruses are most likely to be isolated from acute serum samples obtained within 5 days after the onset of illness. Specific dengue serotypes can be identified by the indirect fluorescent antibody test, with the use of type-specific monoclonal antibodies on the isolated virus, or by demonstrating viral genome by polymerase chain reaction (PCR).

Immunodiagnostic methods for determining dengue infection include detection of antidengue IgM and IgG by enzyme-linked immunosorbent assay (ELISA) and detection of haemagglutination inhibition antibody (HI). Dengue-induced HI cross-reacts broadly with other flaviviruses such as yellow fever and St Louis encephalitis viruses. Complement fixation and neutralization antibody tests are more specific than haemagglutination inhibition. Most serological screening for dengue infection is now done with an IgM ELISA. With appropriately timed samples, the sensitivity and specificity of this test in diagnosing dengue infection appears to be high.

Serologic diagnosis is achieved by IgM antibody-capture by enzyme-linked immunosorbent assay (MAC-ELISA) in two blood specimens taken in a period of 14 days from each other. The first specimen, taken up to the seventh day of the disease, can also

be useful for virus isolation by inoculation of *A albopictus* cells or adult mosquitoes, with specific identification of virus by immunofluorescence tests employing monoclonal antibody reagents.

The pattern of HI response has been used to classify dengue infections as primary or secondary, based on the concept that initial, or primary dengue infections tend to elicit lower HI titres than do secondary infections (subsequent infections with a different dengue serotype or antigenically related flavivirus). IgM:IgG ratios as determined by ELISA may be an alternative method of distinguishing primary from secondary infections. The rise in neutralizing antibody in primary infection is believed to be relatively type-specific and can be used to determine the infecting serotype. In secondary infections, because the immunologic cross-reactivity to different flaviviruses and anamnestic responses may result in heterologous titre elevations, the only reliable method for determining the infecting serotype is virus isolation.

Diagnosis of dengue infection is best accomplished by obtaining an acute serum sample within 5 days after the onset of illness for virus isolation and antibody testing and a convalescent serum sample 14 to 21 days after illness onset for detecting IgG antibody titre rise and/or the presence of antidengue IgM.

Postmortem diagnosis is made by virus isolation or by demonstration of viral antigen (direct immunofluorescence) from two-specimen visceral fragments (liver, spleen, lymph nodes, thymus).

Treatment

As dengue is a viral infection, no

specific treatment is available. Management is mainly symptomatic with early institution of supportive treatment with fluids replacement and correction of electrolyte imbalances which is the key to management of patients with dengue in all its forms, since high fever, anorexia, vomiting and capillary leakage result in some degree of dehydration. Transfusion of fresh blood or platelets to combat bleeding problems and oxygen therapy for low blood oxygen levels may occasionally be necessary.

Patients should be encouraged to drink plenty of fluids. Acetaminophen may be taken to control fever and body ache. Aspirin is contraindicated both because of its anticoagulant effects and the increased risk of developing Reye syndrome. Patients or parents should be carefully instructed of the need to seek medical attention immediately if major or ongoing haemorrhage, signs of impending shock or any change in mental status should occur. The onset of cardiovascular collapse in patients who develop DHF may be sudden.

Patients with significant haemorrhage or signs of increased capillary permeability such as haemoconcentration, effusions, oedema or low serum albumin, as well as patients with mental status changes or with abnormal fluid and electrolyte balance, should be hospitalized and may require admission to an intensive care unit. Isolation is not necessary in mosquito-free environments. The usual precautions handling blood specimens should be observed.

Intravenous fluid therapy is the mainstay of treatment for patients with DHF. Patients with dehydration and haemoconcentration may require

intravenous fluids similar in volume and composition to regimens used to treat dehydration due to diarrhoeal illness. Patients in shock should be given fluids and other therapy according to accepted regimens for shock. The administration of heparin may need to be considered in patients who develop disseminated intravascular coagulation.

Prognosis

With early supportive treatment and aggressive medical care, the majority of cases recover rapidly and without sequelae. Hospitalized patients can return home after 2 days without fever; all patients often experience prolonged convalescence with generalized asthenia and depression lasting several weeks. Untreated patients in shock have approximately a 50% mortality rate.

Prevention

A aegypti is an anthropophilic, domestic mosquito which lives intimately with its human hosts. These mosquitoes breed primarily in man-made containers such as water storage containers, old tyres and flower vases in and around human dwellings. Elimination of these breeding sites is an effective and definitive method of controlling the vector and therefore of preventing transmission of dengue. Nonresidual insecticides such as malathion, which kills mosquitoes on contact, have often been used in attempts to control dengue epidemics. However, non-residual insecticides applied from truck-mounted and aerial equipment may be ineffective when mosquitoes hide within closed houses. New efforts are focusing on community education and behaviour modification in an attempt to encourage neighbourhoods

to control the vector through breeding site reduction.

There is no dengue vaccine currently available for widespread public health use. Research continues on developing an effective and safe tetravalent vaccine that would circumvent the potential hazards predicted by the immune enhancement theory. Currently the only effective way to avoid dengue infection in areas where the disease is endemic or epidemic is to avoid being bitten by infected mosquitoes through the use of personal insect repellent, protective clothes and other insect barriers.

It is important to remember that *A aegypti* is a domestic mosquito, bites during the morning and evening and has a low fly-autonomy (about 200 m). Spraying permethrin or other similar insecticide repellent on clothes, mosquito nets and in bedrooms would effectively reduce man-mosquito contact.

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Clinton Tells of Techno-Terror Peril

■ **Security:** President addresses Coast Guard graduates by warning of evolving global threats. He announces plan to better fund a preventive effort.

By JAMES GERSTENZANG
TIMES STAFF WRITER

NEW LONDON, Conn.—President Clinton warned Wednesday of an angry sea of new dangers facing the United States in the 21st century, from evolving cyber-terrorism to miniature weapons of mass destruction, and announced a plan to add \$300 million to the nation's counter-terrorism campaign.

Offering the prospect of "a fateful struggle" between global harmony and chaos, the president said that the technological advances that made possible the Internet and the Human Genome Project also make "the tools of destruction deadlier, cheaper and more available, making us more vulnerable to problems that arise half a world away."

On a sunny day of brisk, sea-borne breezes bearing not a hint of such malice, Clinton presented a dark picture of malevolence lurking in the new technology as he addressed the 190 cadets graduated in the U.S. Coast Guard Academy's first class of the dawning century—one-third of them women.

Clinton cited the nation's experience at the arrival of the new millennium, when, with the aid of Jordan, "we shut down a plot to place large bombs at locations where

Americans might gather on New Year's Eve."

"We learned this plot was linked to terrorist camps in Afghanistan and the organization created by Osama bin Laden," the president said, reiterating assertions by senior officials linking the threat to the man the United States holds responsible for the fatal blasts at U.S. embassies in Tanzania and Kenya in 1998.

"A short time later, a customs agent in Seattle discovered bomb materials being smuggled into the U.S., the same materials used by Bin Laden in other places," the president added.

Behind Clinton as he spoke rode symbols of the Coast Guard's historic mission and its future: a 40-year-old cutter and a new state-of-the-art patrol boat, both white with the traditional red stripe across the bow, tied at a pier on the Thames River, New London's outlet to the Long Island Sound, the Atlantic Ocean and the world.

It is a world, Clinton warned, offering new threats to the nation:

Computers, on which the world places ever greater reliance, are subject to viruses that can halt global commerce, such as the "love bug" that ran rampant through computers two weeks ago.

Biological, chemical "and maybe even nuclear weapons" can, in the hands of terrorists, bring chaos to the world, he said.

Health threats such as AIDS and malaria "can ruin economies and threaten the very survival of nations and societies," Clinton said.

Global warming and narco-terrorism loom.

He warned too of the risk posed

by nations and organizations seeking the expertise of nuclear weapon scientists in Russia, whose average salary is less than \$100 a month.

The new reality, the president said, is that globalization and information technology "have magnified both the creative and the destructive potential of every individual, tribe and nation on our planet."

But the solution, he said, is neither a "survivalist foreign policy" that turns the oceans into protective moats around the United States nor a "go-it-alone foreign policy," but rather international cooperation and preparation.

Without the cooperation of Jordan and Canada in halting the threat from Bin Laden, he said, "we'd have had bombs going off here as we celebrated the millennium."

Clinton's immediate answer is the \$300-million additional budget request, on top of the \$9 billion he is seeking from Congress for counter-terrorism programs in the 2001 fiscal year beginning Oct. 1.

The White House said the money would be devoted to increasing joint terrorism task forces throughout the country that link the resources of the FBI; Immigration and Naturalization Service; the Customs Service; the Bureau of Alcohol, Tobacco and Firearms; the Secret Service; and state and local law enforcement agencies.

The money would also be used to beef up monitoring of the U.S.-Canadian border, expand federal criminal lab examination of potentially fraudulent travel documents, help track terrorist financing and boost the number of federal lawyers assigned to prosecute terrorists.

Doctors Warned on Bioterrorism

■ **Health:** Federal report urges physicians to learn the signs because they will be crucial to nation's ability to respond to germ warfare.

By MARLENE CIMONS
TIMES STAFF WRITER

WASHINGTON—Federal health officials have warned that primary care physicians, hospital emergency rooms and other local health providers must learn to recognize the signs and symptoms of bioterrorism—because they probably will be the first to see them.

The ability to quickly identify the infectious agents unleashed by bioterrorists will be critical to the nation's ability to respond, according to a new, still-unpublished report drafted by a working group of the federal Centers for Disease Control and Prevention.

"This is the case where we've said doctors will have to go back to school," CDC spokeswoman Barbara Reynolds said.

The report, part of the government's continuing effort to prepare for a potential germ warfare threat, was posted over the weekend on the CDC's Internet site. The recommendations have already been accepted by the Clinton administration, Reynolds said.

The plan marks the first time the CDC has joined with law enforcement, intelligence and defense agencies—in addition to traditional CDC partners such as state and local health agencies—to address a national security threat.

The report does not estimate the cost of the proposals. Congress funded bioterrorism planning activities for the CDC for the first time in fiscal 1999, awarding the agency about \$120 million.

The CDC said it will work with state and local health authorities during the next five years to enhance their ability to identify dangerous agents, such as smallpox, anthrax, plague, botulism and hemorrhagic viruses such as Ebola—which has caused several deadly outbreaks in Africa in recent years.

The agency plans to create a network that will link clinical labs to public health agencies in all states and in selected cities and counties. Also, the CDC said it will make sure that state health laboratories and other agencies that would perform initial testing have the proper diagnostic technology.

In addition, the report said the agency will stockpile appropriate vaccines and drugs, establish effective communication and education programs and establish a surveillance system to detect drug-resistant infectious agents. The CDC listed as its top priority the training and education of local health care providers.

If they fail to recognize suspicious illnesses or injuries, the consequences could be "devastating," with the movement of infected people—and transmission of disease—going unchecked, the report said.

"Only a short window of opportunity will exist between the time the first cases are identified and a second wave of the population becomes ill," the report said.

During that brief period, public health officials would need to deter-

mine that an attack had occurred, identify the organism and prevent more casualties through strategies such as mass vaccination or preventive treatment, the report said.

In the event of an attack, signs of disease might not become apparent immediately, since many infectious agents require an incubation period before patients become ill.

Medical personnel must be alert to the possibility of rare, previously unseen diseases before dismissing early symptoms as routine, the report said.

For example, if bioterrorists release variola virus, which causes smallpox, "patients will appear in doctors' offices, clinics and emergency rooms during the first or second week, complaining of fever, back pain, headache, nausea and other symptoms of what initially might appear to be an ordinary viral infection," the report said.

By the time patients begin to die, "the terrorists would be far away and the disease disseminated through the population by person-to-person contact," the report said.

Smallpox was declared eradicated worldwide in 1980, and no one younger than 20 has been vaccinated against it.

However, some "undeclared" stocks of the highly contagious and often fatal virus are believed to be in the possession of U.S. adversaries. For this reason, President Clinton decided a year ago to preserve remaining U.S. samples of the virus.

"Preparing the nation to address this [bioterrorist] threat is a formidable challenge, but the consequences of being unprepared could be devastating," the report said.

Uncle Sam Says...

FEDERAL HIV TREATMENT GUIDELINES.

The goal of highly active antiretroviral therapy (HAART) is to drive HIV to below detectable levels in the blood. That does not mean that there is no HIV in the body; it means the test results are below the threshold of detec-

tion of available viral load tests.

The impact of HAART is measured by clinical state, T-cell, and viral load tests. Experts now recommend using the ultra-sensitive viral load test when available.

The following recommendations

have been culled from current federal treatment guidelines and represent the prevailing view of frontline physicians.

- **Best first-line therapy:** One strong protease inhibitor (PI) plus two "nukes" (NRTIs), or two PIs: Norvir and Fortovase; or Sustiva and two "nukes."
- **Strong evidence of clinical benefit** and/or sustained suppression of plasma viral load is suggested by choosing one drug from Column A and one from Column B. (Drugs are listed in random order.)

Federal HHS Guidelines for Anti-HIV Treatment*

When to Start Therapy:

Clinical State	CD4 + T-cell Count & Viral Load	Recommendation
Symptomatic (Sick AIDS, thrush, unexplained fever)	Any level	Treat
Asymptomatic (no symptoms)	T-cells below 500/mm ³ or viral load above 10,000 (bDNA) or above 20,000 (RT-PCR)	Treatment should be offered. Strength of recommendation is based on prognosis for disease-free survival and patient's willingness to accept therapy.*
Asymptomatic	T-cell above 500/mm ³ and viral load is below 10,000 (bDNA) or below 20,000 (RT-PCR)	Many doctors would delay and observe; some would treat.

*Some experts observe patients with 350–500 T-cells and viral-load levels below 10,000 (by bDNA) or below 20,000 (by RT-PCR).

(+) Federal HHS guidelines are created by doctors, researchers, and industry representatives. They differ slightly from recent International AIDS Society guidelines created only by doctors. IAS guidelines say HAART treatment should begin when viral load is 5,000–10,000, regardless of T-cell count. To get the full HHS guidelines, call 800-458-5231 or download from www.cdcnapa.org.

When to Interrupt Therapy: There are reasons such as drug interactions or pregnancy that may lead you to delay or interrupt HIV therapy. If you stop, stop all anti-HIV drugs at the same time to reduce the risk of developing drug-resistant HIV.

When to Change Therapy: There are several reasons to consider changing a drug regimen, including drug failure, poor absorption, adherence problems, and serious drug toxicity. Bad side effects are a good reason to substitute one or more drugs from the same class (replace AZT with d4T to avoid anemia, for example). If your regimen is failing, a drug-resistance test may help you determine why a given drug regimen is failing and help you select an alternative regimen. Consider changing your regimen when:

- Viral load does not fall below "undetectable" level within four to six months of HAART.
- Viral load is reduced by less than tenfold after eight weeks of HAART. If absorption appears normal and a person is

adhering to the regimen, change in therapy is warranted.

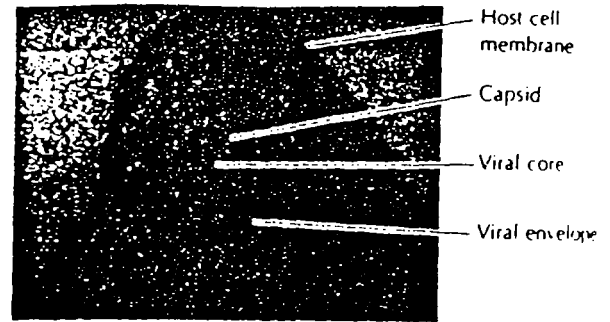
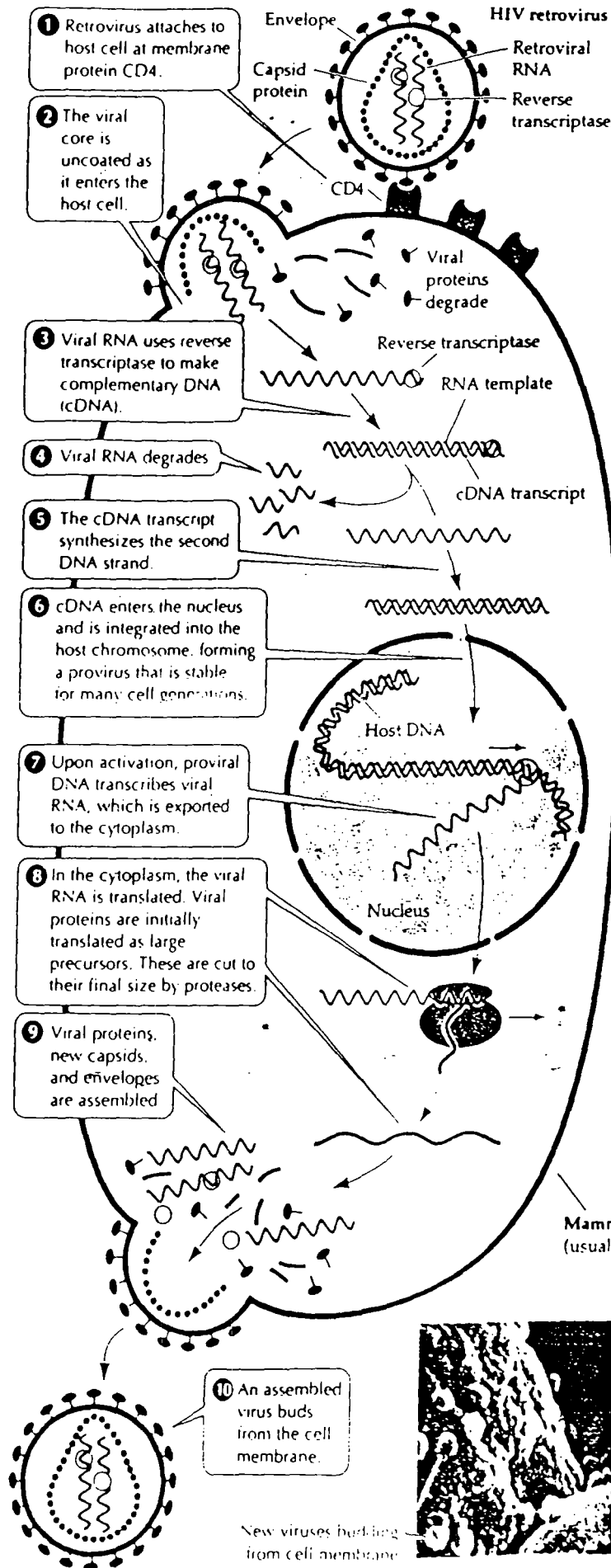
- Viral load increases ("rebound") to above the level of detection after becoming "undetectable."
- Viral load increases threefold or more above the lowest measurement.
- CD4 T-cell count continues to fall.
- Clinical symptoms of HIV disease develop or get worse.
- When switching: Change at least two drugs in your regimen. Ideally, a new regimen should include at least two new drugs that you've never taken before.

When to Delay or Defer Therapy:

Since HIV can become resistant to all HIV drugs, your initial and secondary treatment choices may limit future treatment options. Deferring treatment is an option for those with high, stable T-cell counts, but it's important to get regular medical checkups and monitor your health with viral-load and T-cell tests. If a person is clinically stable, has a detectable viral load, and possesses no good options for changing therapy, it may be best to delay changing therapy in the hope that better drugs will be available in the future.

Column A	Column B
Crixivan	AZT plus ddI
Viracept	d4T plus ddI
Norvir	AZT plus ddC
Norvir plus Fortovase	AZT plus 3TC
Fortovase	d4T plus 3TC
Sustiva	Viramune or Rescriptor with two "nukes"

- **Not generally recommended:** Using only two "nukes" (Column B). They may not be potent enough to suppress HIV and may lead to drug resistance. Avoid Invirase (hard-gel saquinavir); it has been replaced by Fortovase (soft-gel saquinavir).
- **Avoid:** Any monotherapy. This leads to HIV resistance.
- **Avoid:** Adding a protease inhibitor to a failing combination.
- **Bad combinations (drugs that interact poorly):** d4T and AZT; ddC and ddI; ddC and d4T; ddC and 3TC.
- **Short-term goal:** 0.5–0.75-log drop in viral load within four weeks; one log (90 percent) by eight weeks.
- **Long-term goal:** Driving HIV viral load to below the limit of detection ("undetectable") or keeping viral load as low as possible for as long as possible. This prevents drug resistance and allows the drugs to work longer. There is a health benefit to lowering viral load even as little as threefold.
- **Tip:** Use full-dose therapy.
- **Tip:** Consult a doctor with experience in HIV care before starting or changing therapy. Local AIDS organizations have lists of area specialists.
- **Tip:** Discuss side effects, adherence, and drug interactions with your doctor before starting or changing a drug regimen. ■■



diseases of the human central nervous system, including kuru and Creutzfeldt-Jakob disease.

More than 30 years ago Tikva Alper proposed the existence of an infectious agent lacking nucleic acid, on the basis of her work with heavily irradiated infectious tissue. Subsequent work by Stanley Prusiner led to the discovery and naming of the protein fibrils associated with the diseases, but debate has raged for three decades over whether these particles actually are infectious or may harbor a tiny, as yet undiscovered virus. Even if prions are infectious proteins, their mechanism of action is not understood.

Prokaryotes: Reproduction, Mutation, and Recombination

In contrast with viruses, bacteria and archaea are living cells. Prokaryotes carry out all the functions required for their reproduction. They metabolize, they harvest and use energy; they produce and use the molecular equipment that synthesizes both their macromolecules and their small molecules. Accordingly, the genetics of prokaryotes differs from that of viruses—and from that of eukaryotes.

Whereas in eukaryotes genetic recombination results from a melding of the genomes of two par-

xx



13.7 The Reproductive Cycle of HIV The ultimate purpose of the AIDS virus is the prevention of the cell from reproducing. In fact, almost every step in the cycle is designed to prevent the cell from reproducing. The principle behind the development of anti-HIV drugs is to block the virus at various stages of its reproductive cycle.

Original Thinker

Beatrice Hahn

"I REALLY WANT TO ANALYZE ALL THE VIRUSES THAT ARE OUT THERE, WHETHER THEY JUMP TO HUMANS OR NOT."



Timing is everything. Just ask Dr. Beatrice Hahn. When Hahn announced to the world last year that HIV (officially called HIV-1) originally spread from endangered chimps in West Central Africa, she became famous overnight. So did Marilyn and two other *Pan troglodytes troglodytes* chimpanzees who harbored remarkably similar viruses to HIV-1. Here was concrete proof that HIV-1 evolved from ancient simian viruses that had somehow jumped the species barrier. The discovery confirmed a leading theory about HIV's origins—from monkeys to man—and Hahn, 45, couldn't be happier with the publicity that's followed. "People want to know [and] understand what happened in order to prevent future transmissions," she says. Her own work holds

implications for prevention and vaccine studies.

Born in Germany, Hahn got an early start in medicine by accompanying her father, Heinz, a doctor, on visits to patients in rural Bavaria. As a teenager, she liked figuring out why people got sick. "I liked to draw blood," she says, laughing. "He let me do that." She also spent her summers analyzing blood and urine samples in her father's lab until she left for medical school in Munich, and started down a career path to cardiology.

A chance meeting in Munich with Robert Gallo [the codiscoverer of HIV], convinced Hahn to take a chance on coming to the United States to study retroviruses. But there was one hitch to working in Gallo's lab. "He told me, 'Sure [you can come], if you come with your own money,'" Hahn recalls. "It took almost two years, but she got a fellowship, and on May Day 1982, arrived at the National Cancer Institute in Bethesda, Maryland.

A year later, AIDS appeared, although back then it was better known as GRID—Gay-Related Immune Deficiency. When Mikulas Popovic in Gallo's lab cultured and isolated the offending virus, Hahn and coworkers dropped everything to clone it. It was an exciting time, says Hahn. "It was a tremendous opportunity that I was allowed to work on [HIV]," she says. "Things popped up left and right. We pooled together and things just clicked."

A few years later, Hahn moved to Alabama with her lab partner and future husband, George M. Shaw, another leader in the HIV field. Their collaboration continues today. The couple have two "beautiful girls," Katharina, 9, and Christiana, 3.

Hahn comes across as intelligent, intimidating, and a bit in-your-face. As a scientist, she's not afraid to take on the difficult and, at times, controversial and politically charged questions of how, when, and why HIV evolved. "Certain people are afraid of me," she admits, laughing. But despite her success, she denies that she's a mover and shaker. "I'm not interested in politics. I'm passionately interested in science and my family." Nor is she content to sit back and rest on her laurels. "There's still a lot of things I want to find out about monkey virus evolution, so we will have our hands full there. I really want to analyze all the viruses that are out there, whether they jump to humans or not."

While she remains focused on basic science, she also hasn't lost sight of the social impact of the HIV epidemic. "I'm not the saint that starts her career by saying, 'All these poor people, I have to help them,'" she says. "But in all the things that I do, at the end of the day, it would be nice to do something that makes a difference for people suffering from this dreadful disease." —Vicki Burkitt

KATHERINE JONES



Professor of Regulatory Biology, Salk Institute, La Jolla, CA

Current Project: Studying how tat, a key HIV gene, affects virus replication.

Her Take: "Currently there are no good drugs on the market

directed against tat. I see a lot of hope in this area for the future. [In the meantime] get informed, be proactive and be aggressive about health care."

FLOSSIE WONG-STAAL

Professor of Medicine and Biology, University of California, San Diego, CA

Current Project: Focusing on HIV and gene therapy development—trying to find a preventive vaccine and a cure.

Her Take: "Vaccine development is a question of trial and error and we can't afford to wait until one thing fails to try another."



Relief	Lorcet (30 tablets).....	\$40.83
	Hydrocodone/APAP (30 tablets).....	\$14.39
Blood Pressure	Tenormin (30 tablets).....	\$32.66
	Atenolol (30 tablets).....	\$4.29
Blood Pressure	Lasix (30 tablets).....	\$5.98
	Furosemide (30 tablets).....	\$5.49
Antibiotic	Amoxil (30 capsules).....	\$6.73
	Amoxicillin (30 capsules).....	\$6.40
Asthma	Proventil (inhaler).....	\$32.66
	Albuterol (inhaler).....	\$11.24
Pain Relief	Darvocet-N (30 tablets).....	\$23.47
	Propoxyphene N-APAP (30 tablets).....	\$8.21
Antibiotic	Keflex (30 capsules).....	\$49.71
	Cephalexin Monohydrate (30 capsules).....	\$7.46
Anxiety/Panic Disorder	Xanax (30 tablets).....	\$27.10
	Alprazolam (30 tablets).....	\$5.49
Pain Relief	Motrin (30 tablets).....	\$7.13
	Ibuprofen (30 tablets).....	\$5.49
Pain Relief	Tylenol/Codeine 3 (30 tablets).....	\$12.66
	Acetaminophen-Codeine 3 (30 tablets).....	\$6.33

Sources: Prices from Drugstore.com; drug rankings from Drug Topics

More Competition Coming for Popular Prescription Drugs

Many popular drugs will soon lose patent protection, which means they will no longer have a market monopoly. In most cases, less costly generic drugs hit the market soon after patents expire.

Brand Name	Generic Name	Use	Patent Expires
Pepcid	famotidine	duodenal ulcers	Oct 17, 2000
Prozac	fluoxetine HCL	depression	Feb. 2, 2001
Prilosec	omeprazole	duodenal ulcers	April 1, 2001
Mevacor	lovastatin	cholesterol	June 15, 2001
Zestril	lisinopril	hypertension	Dec. 30, 2001
Axid	nizatidine	duodenal ulcers	April 12, 2002
Relafen	nabumetone	arthritis	Dec. 13, 2002
Blaxin	clarithromycin	respiratory infections	May 23, 2003
Diflucan	fluconazole	infection	Jan. 28, 2004
Claritin	loratadine	allergies	April 21, 2004

The Price We Pay

By LINDA MARSA
TIMES STAFF WRITER

Alden Bohlig spent his life teaching teenagers mathematics, so he knows when the numbers don't add up. Why spend up to \$30 a month for a brand-name arthritis drug when he could pay only \$5 by taking the generic version instead?

By substituting generics for his arthritis and other medication he takes regularly, Bohlig says he saves about \$85 each month. "Why pay a premium for the same thing?" asks the 82-year-old retired school teacher from Long Beach. "I appreciate that the drug companies invest money in research. But I don't want to fatten their bank accounts at my expense."

Bohlig is on to something. Like millions of other Americans, he's fed up with the rising costs of prescription drugs, which have been growing four times faster than the rate of inflation. These price hikes are a bitter pill for many of the elderly, who consume the lion's share of prescription drugs, and their plight has become a hot issue in the presidential campaign. But the increases affect everyone, especially those with chronic illnesses and the uninsured.

While health insurers have expanded coverage for prescription drugs, 31% of California's 7.5 million Medicare beneficiaries and 23% of those younger than 65 still have no drug benefits, according to a recent study. And consumers with coverage are affected more indirectly, through higher co-payments and deductibles, and escalating insurance premium costs.

Largely overlooked in the heated debate over drug spending are simple steps consumers can take today to save money. One recent study found that a 10% increase in generic drug use in the United States would cut drug costs by more than \$11 billion annually.

"Every percentage point of increased usage translates into a savings of \$1 billion annually," says Tim R. Covington, a pharmacist at Samford University in Birmingham, Ala., which released the study last month.

As Bohlig discovered, switching to the generic version of prescription drugs can ease some of the sticker shock at the local pharmacy. When there is no generic substitute,



RICK MEYER / LOS ANGELES TIMES

Alden Bohlig, 82, says he saves about \$85 a month on medications by using generics.

other medicines in a family of drugs, antidepressants or ulcer medications, less expensive. Sometimes, over-the-counter remedies like Motrin or Zantac can be substituted for their costlier, prescription versions.

While Americans may complain about rising drug prices, when it comes to purchases, we usually want a Ferrari, not a Daiquiri. Despite an avalanche of evidence to the contrary, there's a lingering perception that generics are somehow inferior to their name counterparts. So perhaps it's surprising that even though about 70% of prescription drugs have generic twins, the share of these drugs has remained frozen at 42% of total U.S. prescriptions since 1990, according to the Generic Pharmaceutical Association, a Washington, D.C.-based trade group.

Some of the skepticism, says Gary L. Lerner, acting director of the Food and Drug Administration's Office of Generic Drugs in Rockville, Md., "stems from consumer impression that if something costs less,

Generics: Savings Over Brand-Name Medications

Continued from S1

be as good." When they go to the drugstore with a splitting headache, the painkiller in the plain wrap just doesn't seem as potent as the brand name, even though they both have the same active ingredient.

This, more than anything else, is a testament to the powers of the placebo effect. Drug makers subtly reinforce this psychology each time they introduce newer, more expensive drugs, which their ads claim are vast improvements over existing treatments to justify the inevitable price hikes. "But newer doesn't always mean better," says Dr. Carol Ben-Maimon, chairwoman of the Generic Pharmaceutical Assn.

Doctors Are Used to Brand-Name Drugs

Doctors are brand-happy, too, and get seduced by the "newer and pricier equals better" sales pitches made by savvy drug makers, according to a study released this month by the Mount Sinai School of Medicine in New York. The researchers found that doctors are often uninformed about the price of medicines and unaware of less costly alternatives that were equally effective.

"So, much of what physicians learn about drugs comes from the weekly visits of the Kens and Barbies," says Robert Seidman, vice president of pharmacy for Blue Cross of California. These are the pharmaceutical company salespeople whose job is to push their products, not those of their rivals. They shower doctors with free drug samples, in part to encourage them to prescribe the product.

Once patients, especially those in fragile health, become accustomed to a particular drug, doctors are reluctant to change a winning formula. Reinforcing brand preferences is the direct-to-consumer advertising of medicines, which boosts brand-name awareness and induces consumers to ask for the

Drugs That Need Careful Consideration

Narrow therapeutic index drugs (NTIs) must be carefully monitored in each patient to ensure they are safe and effective. Here's a list of the most common NTIs.

Brand Name: Tegretol

Generic: Carbamazepine

Use: to control seizures

Brand name: Theo-Dur

Generic name: Theophylline

Use: oral bronchodilator to treat asthma, bronchitis, emphysema

Brand Name: Lithonate

Generic Name: Lithium Carbonate

Use: treats manic depression

Brand name: Coumadin

Generic name: Warfarin sodium

Use: anticoagulant (blood thinner)

Brand name: Dilantin

Generic name: Phenytoin sodium

Use: treats epilepsy, controls seizures

Brand name: Procan ST

Generic: Procainamide hydrochloride

Use: treats severe irregular heartbeats (arrhythmias)

Brand name: Lanoxin

Generic name: Digoxin

Use: treats congestive heart failure, irregular heartbeats

drug by name. The ads are everywhere: Television spots extol the wonders of Meridia, an appetite suppressant, or the ulcer drug, ProliSec, while glossy magazine spreads laud the benefits of drugs like Claritin, which combats allergy symptoms.

The campaigns have earned billions for the industry. The 25 most-advertised medicines accounted for 40% of the rise in retail drug spending in 1999. But these drugs aren't necessarily superior to rivals—they're just better promoted.

Despite generics' dowdy image, they really do behave in the body like their glittery, brand-name counterparts and are subject to the same regulatory scrutiny by the FDA. They must contain the same active ingredient as the brand-name product, and generic drug makers have to prove their product is just as safe and effective with the same quality, purity and potency.

"Our testing assures that the products are interchangeable," says the FDA's Buehler.

About the only time problems could crop up is with the tiny handful of drugs that have narrow therapeutic margins. What this means is that the rate at which the drug is absorbed into the blood

stream has to be carefully monitored, and small variations can make a huge difference. If too much is taken up, the drug could be toxic, while too little can hamper its effectiveness.

"Once someone is stabilized on a particular drug regimen, it's best to stick with that product," says Fred G. Weissman, associate dean for academic affairs at the USC School of Pharmacy.

Generic Costs Tied to Patents on Formulas

The reason why generics are cheaper has nothing to do with quality—it's just the way the patent laws work. Normally, a brand-name company spends anywhere from \$300 million to \$500 million to shepherd a new drug through the lengthy development process. Consequently, drug makers are granted a 20-year patent on these novel formulas, which gives them the exclusive right to sell the drugs while the patent is in effect so they can recoup their investment.

When the patent expires, however, other companies can sell generic versions that have been cleared by the FDA. Since generic manufacturers aren't starting from scratch, their development costs are a fraction of those of the inno-

vators. An injection of good old-fashioned capitalistic competition helps, too: Having more than one product on the market also drives down the price. The savings can be substantial. The average cost of generic drugs in 1999 was \$18.45 versus \$61.33 for a comparable brand name, which can add up to hundreds of dollars a month for people taking several medications. On specific drugs, the differences are even more striking. The antibiotic Keflex has a \$50 price tag while its generic counterpart Cephalexine costs about \$7.

However, some widely used drugs, such as Prozac and Claritin, are still under patent protection and continue to command top dollar. But even if their drug of choice is still under patent, consumers can find cheaper drugs that do the job. Prices on other medications that have the same method of action on the body and are part of the same class—the so-called “me, too” or copycat drugs—may be less. Prilosec, for example, a top-selling antacid, costs \$4 per pill. But tablets of Prontinex, the newest member of this drug family, costs \$2.50 per pill. “‘Me, too’ can represent modest advances—perhaps they have fewer side effects, or you only have to take them once a day instead of every eight hours,” says Samford University’s Covington. “But not always. A lot of times, copycat drugs aren’t any better, and they have to compete purely based on cost.”

With drug prices skyrocketing, there is a growing recognition that using generics makes good financial sense. Many health care plans, like Blue Cross of California, offer financial incentives, such as higher co-payments for brand-name drugs, to members who use generics. A few health plans require members to foot the entire bill for brand-name drugs.

Kaiser Permanente, the giant health plan, has a different approach for its Southern California members, who pay the same co-payment for generic or brand-name drugs. Kaiser doctors, however, are encouraged to prescribe the least costly drug when appropriate. As a result, about 60% of drugs dispensed to Kaiser members are generic—nearly 50% more than comparable rates nationwide. This statistic is revealing because it illustrates a change in doctors’ prescribing behavior in a tightly controlled health care organization



AL SEIB / Los Angeles Times

Pharmacist Harold Washington Jr. displays generic alternatives.

such as Kaiser in an effort to counter the marketing muscle of the giant drug companies.

The National Consumer League, a consumer group headquartered in Washington, D.C., has also mounted a campaign to educate consumers about the benefits of generics and has a pamphlet that answers some of the most commonly asked question about these drugs on its Web site (<http://www.nclnet.org>).

Patients will have more choices soon, as a number of widely prescribed drugs lose patent protection and generic versions reach the market. Patents have expired or

are due to lapse within the next year on such drugs as Prozac, Prilosec and the blood pressure medications Vasotec, Hytrin and Zestril.

‘Last month,’ a bill was introduced in Congress by Sens. John McCain (R-Ariz.) and Charles Schumer (D-N.Y.) to speed approval of generic drugs. The bill, the Greater Access to Affordable Pharmaceuticals Act, is aimed at closing legal loopholes that enable pharmaceutical companies to extend their patent protection and prevent competition.

“They use legal maneuvers to delay the approval of competing generics,” says Travis Plunkett, legislative director for the Consumer Federation of America, a consumer watchdog group in Washington, D.C., that supports the proposed legislation.

Similarly, the Federal Trade Commission said last week that it will investigate whether brand-name and generic drug makers have conspired to delay the sale of less expensive medications. In at least one instance, a brand-name drug maker has paid a generic drug firm millions of dollars to not produce competing products.

Meanwhile, consumers don’t have to blindly follow orders when their doctor writes up a prescription for an expensive medication. They should ask their physician or pharmacist about the most cost-effective drug to treat their disorder. They might discover the less glamorous generic does the trick, which would make prescription drug costs easier to swallow.

Health Staff

Editor:

David R. Olmos, (213) 237-7611

E-mail: david.olmos@latimes.com

Deputy Editor:

Tami Dennis

(213) 237-7611

E-mail: tami.dennis@latimes.com

Art Director:

Stephen Sedam

E-mail: stephen.sedam@latimes.com

Administrative Aide

Cindy Dorn

(213) 237-7788

E-mail: cindy.dorn@latimes.com

News Editor:

Jan Molen

E-mail: jan.molen@latimes.com

Staff Writers:

Jane E. Allen

(213) 237-4817

E-mail: jane.allen@latimes.com

Benedict Carey

(213) 237-7742

E-mail: benedict.carey@latimes.com

Linda Marsa

(213) 237-7117

E-mail: linda.marsa@latimes.com

Shari Roan

(213) 237-7619

E-mail: shan.roan@latimes.com

Please include your address and phone number on letters to the editor sent by fax or e-mail. We welcome comments and suggestions but regret that we cannot respond to individual queries.

E-mail: health@latimes.com