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Neutropenia Support Assoc. Inc.

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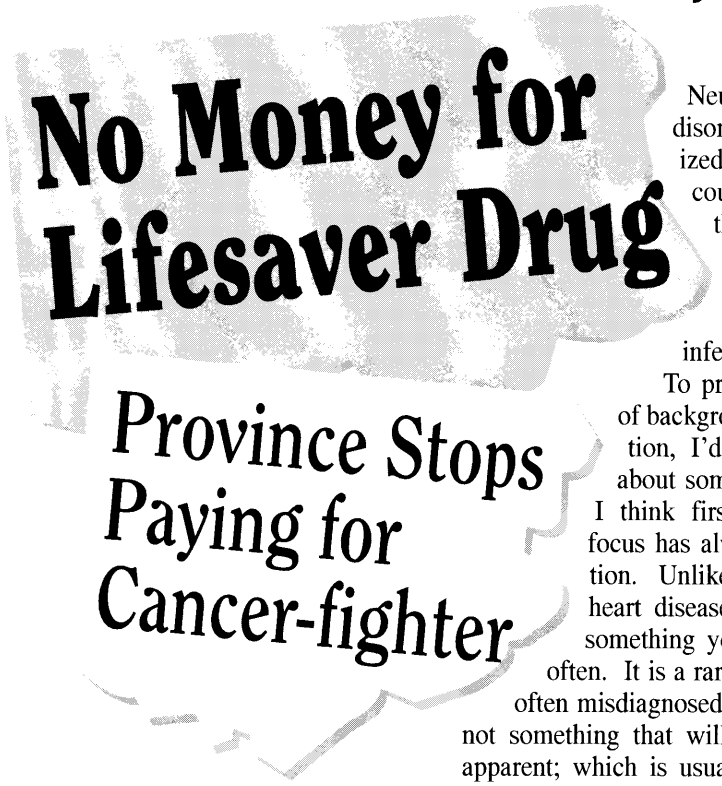
Opening Remarks by Lorne Stevens 4th Annual Fashion Show luncheon October, 1995



Headlines from Winnipeg Free Press September, 1995

Neutropenia is a blood disorder that is characterized by a low neutrophil count. Neutrophils are the white blood cells in our system which are responsible for fighting bacterial infections. .

To provide you with a bit of background on our organization, I'd like to talk briefly about some of our early goals. I think first and foremost our focus has always been on education. Unlike cancer, diabetes, or heart disease, neutropenia is not something you come across very often. It is a rare disease; in fact it is often misdiagnosed, simply because it is not something that will make itself readily apparent; which is usually the case when a physician is trying to make a difficult diagnosis. We have managed to amass a substantial amount of information on the subject and are happy to provide that information to anyone that asks. We have received calls from across Canada as well as internationally. Recently we received a request via our E-mail from Israel. It's most gratifying to know that our work is becoming known and is being appreciated.

Another goal we had in the early stages of our group, was the federal approval of a new drug that had shown great promise in the treatment of neutropenia and chemotherapy induced neutropenia. We spent many hours on the phone with numerous government departments, physicians, as well as media in an effort to play an advocacy role in speeding up the approval process of this new drug. The drug, which is known by the brand name of Neupogen, was eventually approved.

After Neupogen was approved, as a group, we very pleased about overcoming what we felt would be our biggest hurdle. A treatment for neutropenia was now available and we could focus our attention on other issues. It was shortly thereafter, that someone, (someone that knows the health care system very well) said to us that our real work was still ahead. And we were a little naive at the time and thought our major battle had already been won. He was right because, being a new drug, Neupogen is expensive, and when you are dealing with a new drug that is also very expensive, decisions that should be made in a medical setting are now being made on a political level.

About Sept. of 1995, I'm sure you all recall the decision to cut the funding for certain cancer drugs for children. If the child had been diagnosed before Sept. 4 funding would continue. If you were unfortunate enough to

continued next page

Opening Remarks *(continued)*

be diagnosed after Sept. 4 well ... that was too bad. The story was front page news, the Minister of Health was taken to task in the Legislature and the decision was overturned in very short order. Thank goodness we live in a society that will not allow children to die in order to save money when a proven treatment is available. There were two drugs involved in this controversy - one was Neupogen ... and it's new, and it's expensive, and it's now political.

So now we find ourselves playing the role of watchdog to some degree. It's no secret that our health care system is in trouble; everywhere we turn it seems we are being faced with a new round of cutbacks. Hard decisions need to be addressed and its important that all of the facts are available to those in the decision making process.

When a drug like Neupogen comes under scrutiny it's easy to say "We can't afford it. It's too expensive". Despite the fact that it works very well there is no getting around the cost factor. But this is where the decision makers have to look at the big picture and the long term gain. Simply put ... a years supply of Neupogen for a pediatric chemotherapy induced neutropenia patient costs about the same amount as a weeks stay in hospital. We have ample documentation showing that denial of a drug, such as Neupogen, to someone with neutropenia will result in an extended stay in the hospital. The net result being that it costs more money to deny the drug rather than providing it to those who can benefit from it. Does this make sense to you ? It is time we looked at these types of tradeoffs in an attempt to make the right decisions for long term gain instead of short term Band-Aid measures. ■

Editor's Note: We continue to be watchdogs now that Pharmacare and the Lifesaving Drugs Program this spring have basically been dismantled. We predicted these changes last fall and continue to commmunicate with policy and decision makers. Your views are welcomed.

Fourth Annual Fashion Show Another Big Hit!

With your overwhelming support we reached the 4th anniversary fashion show luncheon goal of $5,000.00 with $500.00 going to the Firefighter's burn fund. Many local businesses made donations to the auction. Seven clothing retailers were featured. B.M.D. Talent Inc. helped organize our "best ever" event. All models donated their time and energy!! Entertainment by the Greasettes (lip synch winners) added to the event. Many Thanks to You All!!

Our guest speakers were Dr. Nathan Kobrinsky and Dr. Bonnie Cham.

Excerpts from Dr. Kobrinsky's presentation:

Neupogen is absolutely necessary for individuals with congenital Neutropenia and chemo therapy induced Neutropenia. There was a time when the Red Cross was mandated to provide blood products to those in need. We are now approaching a time when hopefully blood products will no longer be necessary. There is an attempt now to eliminate all blood products. White blood cells can now be produced using Neupogen and the technology is available to produce red blood cells as well as platelets. The direction in the future is toward less blood, hopefully no blood, and relying on all recombinant and genetically engineered hormones. Today we have the technology, but not the money. As more and more of these drugs becomes available the cost goes up and the political implications increase as well. As long as those in need of these products are dependent upon the decisions of governments, as well as suppliers outside of Canada, there will always be uncertainty.

I urge we push towards growth factor independence in manufacturing and supplying these products. This technology needs to be brought to Canada. There needs to be a national effort so that all of these products are available to all Canadians. This is the future for all kinds of patients.

As good a job as the Red Cross has done, it needs to be put into an historical perspective. To do that is not an easy task. We cannot look to government because there is no money.

If we can adopt the kind of vision that exists within the Neutropenia Support Association perhaps it is possible that Canadians can have a source of growth factors for all Canadians. To make this a national priority, I think, is ultimately the thrust of this organization. It would free individuals from their dependency on pharmacy so that the crisis of September 1995 can be eliminated.

There are other issues that can also bring about cost saving measures such as the present dosing and packaging of Neupogen which results in some of the drug having to be thrown away at a cost of hundreds of dollars.

Appropriate levels of white blood cells need to be determined in order to provide proper titration of Neupogen.

The potency, that is the killing power, of white blood cells can be increased thorough the simple use of Vitamin C. This has been proven in the laboratory. This would lead to lower white blood cell counts, but those white blood cells would be stronger and therefore lower doses of Neupogen would be necessary.

Strategies like these need to be supported now. I would also call on you to support the longer range plan of Canadian independence for growth factors.

* * *

Excerpts from Dr. Cham's Presentation:

The Neutropenia Support Association has become the facilitator for the development of the National Neutropenia Network in the States as well as raising funds and advocate for patients with Neutropenia and chemotherapy induced Neutropenia all across Canada.

Neutropenia is a decrease in the number of neutrophils circulating in the blood which fight bacterial and fungal infections. A person can be born with Neutropenia or develop it later in life. The causes of Neutropenia can vary from as simple as a viral infection which can cause the bone marrow to temporarily shut down neutrophil production to those people who have an inability to produce any neutrophils. The effects of Neutropenia can be mild or can be very serious.

Neupogen has been proven to significantly improve quality of life, including a feeling of well being and an improvement in their socio-economic position in life.

This is only the beginning. We need to find more effective ways to administer the drug as well as to find out more about the disease, it's treatment, and it's long term effects.

In the past, many Neutropenia patients were seen by family physicians who may have never encountered Neutropenia before. We therefore have no idea what the true incidence is.

With this in mind, in 1993, a group of interested physicians were brought together to establish the Severe Chronic Neutropenia Registry. Patients have now been enrolled in the registry since March 1994 and 324 patients have been enrolled world wide. This is essential to establish a physician network and to assist in the treatment, management, and to understand the disorder. It will also help to establish a database for future research.

We have made great strides in the past 6 years and will continue to monitor progress in order to move forward. I would like to thank the Neutropenia Support Association in helping us raise awareness and promote education through events such as this fashion show.

* * *

We awarded Charity Builder certificates to recognize the many valuable volunteer contributions.

Again our energetic and dynamic duo, Lorna Stevens and Janis Benzelock came through as chairs of this major undertaking. Our out of province and U.S. guests made this our 1st international fund-raiser as we celebrated Manitoba's 125th Anniversary. Your continued support has enabled us to provide $50,000 to research and over $30,000 for ongoing Neutropenia education. This includes our newsletter, distribution of information packages, internationally maintaining our nation wide toll free info-line, promoting physician presentations, and patient advocacy.

The event also launched a line of hasti notes featuring artwork by children receiving treatment from the Manitoba Cancer Treatment and Research Foundation.

Editor's note: The "Caring Cards" hasti notes are a new fund-raiser. We received assistance from Dawn Kidder (MCTRF) and Ellen Good (Children's Hospital). Burger King provided a thank you gift for all participants.

The artists were guests at the luncheon. The funds raised will specifically be earmarked for pediatric chemotherapy induced Neutropenia education and treatment needs. A package of 6 sells for $5.00. Please use the tear off form for your order. Thank You!

If you are interested in selling them for us, please give us a call. ■

Jamie Benzelock "Prize Runner" and Lorna Stevens "Co-chair"

Janis Benzelock "Co-chair"

Our "M.C."s, Tom Milroy and Lorne Stevens

The Greasettes

(left) B.M.D. Talent

Words from Shirley Cox

A COPY OF THE SPEECH GIVEN TO THE NEUTROPENIA SUPPORT ASSOCIATION INC. FASHION SHOW FUND RAISER IN WINNIPEG MANITOBA, OCTOBER 30 1995, BY SHIRLEY COX - CHAIRPERSON OF THE ONTARIO CHAPTER OF THE NEUTROPENIA SUPPORT ASSOCIATION.

A simple thank-you, will never be enough to repay each and everyone especially the Neutropenia Support Association, responsible for the changes in my families life. Changes brought around because of the generosity of all of you. Some gave time, some gave money and others gave knowledge. Regardless of whom gave what, each of your lives intertwined with each other were instrumental in saving my family from certain death.

Just a few short years ago, I wondered how I would ever cope. My husband was constantly sick and the memory of our daughter's death was still all too fresh in my mind. We had just received the horrifying news that our youngest son would suffer with Neutropenia throughout his life as his father and sister had and a few months later his new baby brother would be sentenced to the same awful fate. A life if they lived, of pain, suffering and constant worry. Neutropenia not only affects the patient but the entire family. My physical and mental health were under tremendous strain having to care for a chronically ill family. Fear, I called hysterical fear would grow more and more intense with each passing crisis. Fear of somehow bringing home a bacteria that would ultimately kill my husband and two beautiful baby boys.

How could anybody survive and thrive under such circumstances.

But look at what a few people focused on a common goal can accomplish.

Because of your giving of time, your giving of money and your giving of knowledge, my life and the lives of many, many others around the world have been profoundly changed forever.

The fear of a little scrape turning into a life threatening situation are all gone. The fear of having to bury an innocent little child or a spouse is gone. Not just put out of my mind but gone forever, because of all of you and the many more who cared enough to help.

For all that I have received I can only give my heartfelt thank-you, for saving my family's life, and a promise. A promise to live out my life helping others like you have all helped me. **Giving is Rewarding.**

There are still many hurdles to jump, barriers to break down and a cure to find, but, together.... Our Neutropenia Family, is a circle of strength, with every birth and every union, the circle grows. Every joy shared adds more love, every crisis faced together, makes the circle stronger.

The Neutropenia Support Association have aided many families like mine, and with continued support from you, will be able to continue there volunteer work for years to come.

(l-r) Spencer, 4, Travis, 5, Cox's "Neupogenmen"

Many people have made outstanding efforts on our behalf, and for that we all give our Thanks. I brought with me today two cheques from the caring people of the Alliston Street Toys Antique Car Club in Alliston Ontario who wanted you to know, they care too.!

Lorna, I would like to present you with their very generous donation totaling $2800.00.

I will close now with a poem for you to ponder.

One hundred years from now,
It will not matter what your bank account was, the sort of house you lived in or the kind of clothes you wore,
But the World may be much different
Because you were important
In the life of a child.

Shirley Cox
11 David Drive. R.R. # 1

Rare Disease Research gets Boost

Re-print from an article in The Herald, Alliston, Ontario, Nov. 29, 1995
By Catherine Haller, Herald editor.

In just a few years Shirley Cox of Lisle has raised awareness about a rare disease to the point where sufferers no longer live in fear of dying from a simple scrape.

Neutropenia is a rare and life threatening blood disorder that virtually immobilizes the immune system.

Cox' husband and children have the disorder which claimed the life of one of their children.

She found that living in constant fear of even the slightest mishap was more than she could bear. Despite being a constant nurse, with no medical training, to her family she focused on building a support network for people affected by the disorder.

Now chair of the Ontario chapter of the Neutropenia Support Association, Cox told an assembly at a recent fund-raiser in Winnipeg how the association and medical research has changed her life.

Now on a drug which fights the disorder and makes life relatively normal, her family no longer has to worry about every germ and scratch.

"Just a few short years ago, I wondered how I would ever cope," Cox said in her address.

"My husband was constantly sick and the memory of our daughter's death was still all too fresh in my mind.

"We had just received the horrifying news that our youngest son would suffer with Neutropenia throughout his life as his father and sister had, and a few months later his new baby brother would be sentenced to the same awful fate."

She then spoke of the accomplishments of the association, paying tribute to all the volunteers.

"For all that I have received I can only give my heartfelt thank you for saving my family's life, and a promise".

"A promise to live out my life helping others like you have all helped me. Giving is rewarding," said Cox.

She then presented cheques totaling $2,800 donated by Alliston Street Toys, a club of antique and classic car collectors.

The club meets throughout the summer months in Alliston and raised the money through 50/50 draws.

Although Alliston Street Toys wasn't directly represented at the assembly, the club received a standing ovation for its generosity.

Editor's note:
We are sincerely grateful for groups like the Alliston Street Toys and for all the work they and Shirly Cox have done for the Neutropenia Support Assoc. Inc. A big hug goes out to all the people in Ontario for their tireless effort.

Thank-you!!

Giving is Rewarding!!

An update on our past fund-raisers.

1995 Poor Man's Golf Tournament

In aid of Neutropenia & The Rainbow Society, September 21, 1995.
Winnipeg, Laurie Mustard column

For only $50 a head, a host of kind-hearted (and not so poor) souls played golf and risked their reputations at a karaoke after-bash to raise money for the Rainbow Society and Neutropenia at the Transcona Golf & Country Club. Enter Bob LaFleche, who blew everybody away with a professional-level singing performance. Other wild 'n' crazy performers included CJOB's Jim Benzelock, Sun Life guy (and former model) Reg Matheson, whose team won the event, karaoke host Campbell McIntyre of Empire, Lorna Stevens from Neutropenia and Jets alumni Ab McDonald and Gordie Tumilson.

This event raised $2436.00 for the Neutropenia Support Assoc. Inc.

And More...

Newfoundland contributed over $1,000 from their local fund-raising. Many thanks go out to all that participated.

Ontario generated over $1,500 with their own local fund-raising efforts. Many thanks go out to The Royal Canadian Legion of Ontario, the Rotary Club of Alliston in Ontario

Editor's note..
It is indeed very hard to express our appreciation for all your hard work and efforts that went into the these fund-raisers, and we can't thank you all enough for your many contributions.

* * *

We would also like to thank **The Manitoba Government Employees' All Charities Campaign** for their continued support .

1-204-945-5621

Donors have the opportunity to donate by cash, cheque or payroll/pension deduction to any one or number of charitable agencies of their choice. So don't forget about The Neutropenia Support Assoc. Inc.

* * *

Also Thanks to the **United Way** .

"United Way gives to and gives through service"

and

"Preferred Giving Program"

Our Canadian charitable registration number is 0848093-11.

* * *

We would also like to give a big **"Hardy Well Done Gang"** to the **M.T.S. Pioneer Women and Men** who came to our aid and helped with the distribution of our last newsletter. Your help is very much appreciated, Thank-You!! ■

Hockey Tournament

The **Winnipeg OldTimer's Hockey Club** and the **Winnipeg Jets Alumni** came through big time again with $2880 raised from their annual Hockey Tournament.

Since its inception seven years ago, the organization has supported charities like the Children's Wish Foundation, the Juvenile Diabetes Foundation, the Christmas Cheer Board, Ronald McDonald House and the Neutropenia Support Association. What a great way to enjoy a super sport while upholding our tradition of caring and compassion through volunteerism and community service. Keep up the good work!

Poor Man's Golf Tournament

September 26, 1996

Transcona Golf & Country Club

Auction, lots of prizes, karaoke, food & fun!!

Call Jim & Janis Benzelock 667-0324

We Welcome Golfers and Volunteers

Come and Join Us!

The 7th Annual Winnipeg Jets Alumni Heritage Golf Classic

Winnipeg Oldtimers Hockey CLub

To benefit Winnipeg Jets Alumni Kidsport Fund and Neutropenia

Thursday, June 20th, 1996
at the Kingswood Golf Club
La Salle, Manitoba

Tee Off: 1:00 pm sharp

Golf Fee: $125.00 ($40.00 charity tax receipt)

All inclusive day; prizes, dinner, refreshment.

Call Jordy Douglas 885-6865 for more information.

Pharmacoeconomics and Oncology Workshop

Held November 22, 1995

Our president, Lorna Stevens, attended this workshop. The specific objective was to focus on issues regarding ONDANSETRON and FILGRASTIM (Neupogen) in the treatment of febrile Neutropenia.

60 % of Neupogen's coverage was off loaded onto Pharmacare effective January 1, 1996.

Manitoba Pharmacare changes effective April 1, 1996

Those currently enrolled in the life-saving drugs program need to be aware this program is under extreme transition. The Manitoba "Drug Use Management Centre "DUMC" may include Pharmacare, MHO, ISM (owned by IBM) and others as part of the "Network". We are aware the confidentiality of medical and financial information available to private industry may be of concern.

There is also concern that formula drugs will be approved on the basis of pharmacoeconomic guidelines and could be contingent upon financial participation with drug manufactureers. This raises the question of whether a drug is being approved on its merits or because of financial participation by the pharmaceutical company. The second question raised recently in a Pharmacy newsletter asked their members to express their feelings regarding access to all individual medical and financial records to the private sector.

Should you have any difficulty with your prescription please let us know as we are trying to monitor the situation. Your comments are welcomed. ■

Alberta Blue Cross

A Reminder about Alberta Health Non-Group plan maximums

For Groups 1, 66, 66A, there is a $25,000 maximum per plan participant for drugs and extended health benefits (including ambulance) per benefit year.

Each benefit year runs from July 1 to June 30

The Alberta Health Drug Benefit List

1. the Alberta Blue Cross Non-Group Coverage (Group 1)

2. the Alberta Blue Cross Coverage for Seniors (Group 66)

Alberta Widows Pension Plan (Group 66A)

Special Authorization of Certain Drug Products

Some drug products may be considered for coverage by special authorization for patients covered under Alberta Health-sponsored drug program. For criteria for coverage of Alberta Family and Social Services clients, please refer to the Special Authorization section of the Alberta Family and Social Services Drug Benefit Supplement.

Criteria for Coverage:

Neupogen (Filgrastim) injection

To decrease the incidence of infection, as manifested by febrile Neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs. *This drug product must be prescribed by the Directors of Alberta Cancer Board Centres (or their designates).*

To increase neutrophil counts and to reduce the incidence and duration of infection in patients with diagnosis of congenital, cyclic or idiopathic Neutropenia. *This drug product must be prescribed by the Directors of Divisions of Hematology in tertiary care centres (or their designates).* ■

ONTARIO NEWS

Working Poor to Receive Help with Their Drug Cost

Seniors earning less than $16,000 (and couples less than $24,000) and social assistance recipients will pay only a $2 co-payment for each prescription filled. Seniors earning over those amounts will pay the first $100 in prescription costs each year per person, then the Ontario Drug Benefit dispensing fee of up to $6.11 per prescription.

"We are also revising the Trillium Drug Program to make it easier for people earning less than $20,000 to become eligible for drug benefits, "More working poor will now be able to get assistance with their drug costs without having to quit their jobs."

The changes will be effective starting June 1, 1996

Anyone having questions about these changes can call the Ministry of Health INFOline at 1-800-2681154

In The London Area

Neutropenia was the topic in the academic sessions of 3 departments (pediatrics; microbiology & immunology; internal medicine). These 3 departments jointly sponsored a visit by Dr. Dale - he gave a few excellent seminars while in town. Some London doctors were co-investigators on a study that he presented. In pediatrics, they organized a whole week's resident training schedule around hematology. It was an excellent effort. ■

SCN International Disease Registry

We still only have a fraction of Canadian patients registered thus far.. PLEASE urge your Physician to register.

Here are some questions & answers regarding the Registry:

What is the benefit of the Registry to a participating physician?

- Will become part of a physician network designed to increase the understanding of SCN
- May request information from the Registry
- Is eligible to submit research proposals to the advisory board for evaluation
- Will receive periodic summaries and analyses of aggregated data from the Registry as an aid to clinical management and research

What is the SCN International Registry?

The SCN International Registry is a disease registry which was established in Australia, Canada, the European Community and the United States and initiated in March 1994. This Registry is directed by a scientific advisory board of physicians from around the world who care for SCN patients. The mission of the Registry is to establish a worldwide database of treatment and disease related outcomes for persons diagnosed with SCN. Collection of this information will lead to improved medical care and become a focus for future research.

Who is eligible to participate?

All individuals three months of age or older who have a physician's diagnosis of SCN are eligible to enroll in the SCN International Registry.

A diagnosis of SCN must be documented by:

1. Clinical history of absolute neutrophil counts <500/mm3 over a three month period
2. A bone marrow evaluation consistent with SCN
3. Cytogenetic evaluation and
4. History of infections

Non-eligible patients include those with:

- Drug-induced neutropenia.
- Thrombocytopenia (platelet count less than 50, 000/mm3) or anemia (hemoglobin less than 8 gm/dl).
- Myelodysplastic syndrome, aplastic anemia, known HIV infection, or other hematologic diseases.
- Known immune diseases such as rheumatoid arthritis and systemic lupus, and autoimmune neutropenia.
- Chemotherapy-induced neutropenia.

Why was the Registry created?

- To establish a worldwide database of treatment and disease-related outcomes for persons diagnosed with SCN.
- To monitor the long-term safety of treatments in SCN patients.
- To use information gained through the Registry to improve the medical care of SCN patients.

Severe Chronic Neutropenia International Registry

Contact Physicians & Local Liaison Physicians

For Patients in Canada:

Dr. Bonnie Cham
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Neutropenia Support Assoc. Goes to the A.S.H. Conference

"I picked up a copy of your Neutropenia Support Assoc. bulletin at the recent ASH meeting. Will you please add my name to the mailing list"

This was a typical response after the A.S.H. Conference. Lorna Stevens, Neutropenia Support Assoc. in Canada, and Silke Deeley, National Neutropenia Network, United States, shared a room and attended over 20 sessions. These are some of the sessions identified by Lorna to be of particular interest.

SEVERE CHRONIC NEUTROPENIA: REPORT ON TREATMENT AND OUTCOME FROM A NEW INTERNATIONAL REGISTRY

DC Dale, T Cottle, AA Bolyard. C Fier, MA Bonilla. L Boxer. SL Brown. B Cham, M Freedman. G Kannourakis. K Welte, for the Severe Chronic Neutropenia Registry, Seattle, Washington; Hannover, Germany

The Severe Chronic Neutropenia International Registry (SCNIR) was established March 1994 to further understanding and improve care for congenital, cyclic and idiopathic Neutropenia. For enrollment patients must have an absolute neutrophil count (ANC) chronically less than 0.5 X 10 9 /L. The Registry is directed by a panel of expert physicians and receives support from Amgen, Thousand Oaks, California. To date, there are 294 patients *(editor's note: now 324)* enrolled in the SCNIR, U.S. 169, Germany 37, Australia 25, United Kingdom 14, Canada 11, Italy 10, Belgium 7, Netherlands 5, France 4, Israel 4, Republic of Palau 1. By diagnosis, 56% have congenital, 23 % cyclic and 21 % idiopathic Neutropenia.

Registry data show that 279 of 294 enrolled patients are now receiving therapy with G-CSF; of these, approximately 64% have received this therapy for greater than 5 years. Only about 9% have received other therapies - GM-CSF, corticosteroids, gammaglobulin, and none are receiving these therapies long term. G-CSF dosing

Dr. Lawrence Boxer, Ann Arbor Michigan, and Dr. David Dale, Seattle, Washington

varies by diagnosis: congenital, median 8.0 mcg/kg/day, range 0.15-60 mcg/kg/day; cyclic, median 3.0 mcg/kg/day, range 0.5-12 mcg/kg/day; idiopathic, median 1.4 mcg/kg/day, range 0.1-8 mcg/kg/day. The majority (68%) receive G-CSF on a daily basis. The goal of therapy is to maintain blood neutrophils at 1.5-10 X 10 9 /L. Only two Registry patients, one congenital and one idiopathic, have not responded to G-CSF therapy, and have proceeded to marrow transplantation. Cumulative data on adverse events in this population, largely patients on long term G-CSF treatment, shows thrombocytopenia occurring in 6% and vasculitis 3%. The hazard rate for the development of myelodysplasia (MDS) or AML is approximately 3% at five years for patients with congenital Neutropenia. MDS or AML have not been observed in patients with idiopathic or cyclic Neutropenia. Continuing observations and research utilizing the Registry will serve to clarify the mechanisms and optimal treatment for these unusual disorders.

Silke Deeley N.N.N., and Lorna Stevens, N.S.A.I., SCN Registry Booth A.S.H.

ADMINISTRATION OF r-metHuG-CSF DURING PREGNANCY IN PATIENTS WITH SEVERE CHRONIC NEUTROPENIA (SCN)

L. Boxer, D.Dale, M.A.- Bonilla, B. Cham. M. Freedman, Kannourakis. S. Brown. C, Fier. and K. Welte., for the SCN International Disease Registry, Seattle WA, Hannover Germany, and Amgen, Thousand Oaks, CA.

rHuG-CSF(Filgrastim) is known to cross the placenta in several species of mammals including man. Review of Amgen records reveal 10 pregnancies among 8 SCN patients during the time they received rHuG-CSF treatment (dose range 1-10mcg/kg/day). This included 4 patients with cyclic Neutropenia and 4 patients with idiopathic Neutropenia. There is no record of a congenital Neutropenia patient becoming pregnant while on rHuG-CSF treatment. We are aware of no data about pregnancy outcomes in this patient population prior to the availability of cytokines. rHuG-CSF was administered throughout gestation during 4 pregnancies. These pregnancies resulted in 2 normal infants; one infant with bilateral hydronephrosis; and one infant with cyclic Neutropenia, born to a mother with cyclic Neutropenia (which has a described autosomal dominant inheritance). There were 4 pregnancies during which rHuG-CSF was administered in the first or first and second trimesters. These 4 pregnancies resulted in one normal infant and 3 therapeutic abortions, including one pregnancy which was terminated because of ultrasound echography that provided evidence of abnormal embryogenesis. In 2 pregnancies rHuG-

ADMINISTRATION OF r-metHuG-CSF
(cont'd)

CSF was administered in the third trimester only. One of these pregnancies resulted in an infant with cyclic Neutropenia who was otherwise normal, born to a mother with cyclic Neutropenia. The other pregnancy resulted in an infant with cardiac septal defects, which likely arose during embryogenesis prior to the administration of rHuG-CSF. In conclusion there are no well-controlled studies of the use of rHuG-CSF in pregnancy. The data from the few case reports in patients with SCN are inconclusive to assure safety regarding the use of rHuG-CSF during pregnancy in this population; therefore, any decisions regarding the use of contraceptives or continued treatment during pregnancy must be made between the physician and patient on an individual basis. Data regarding, pregnancy outcomes in this patient population will continue to be collected through the Severe Chronic Neutropenia International Registry. ■

In the Works

Our booklet "Chemotherapy & Neutropenia" is being translated into other languages, a Portuguese version by ACREDITAR, and an Italian version by The Italian Confederation, part of the ICC-CPO.

We will keep you posted on this one.

***

The N.S.A.I. is interested in receiving all recent articles pertaining to autoimmune and virally-induced neutropenia. ■

Helpful Hints

Syringes for patient kits

There are two sizes (25 gauge and 27 gauge). The larger the number the smaller the diameter of the needle. If someone is prescribed the 1.0 ml vial of NEUPOGEN®, they can use either the 25 gauge or the 27 gauge. However, if one is using the 1.6 ml vial (480 ugm), the 25 gauge will have to be used. The reason being the barrel on this syringe has a volume of 3 ml but the 27 gauge is available only with a 1.0 ml barrel.

Editor's Note: Be sure to warm the vial of the drug just before injection. This will prevent the cold stinging sensation when the drug is injected under the skin. ■

Up and Coming Events

Childhood Cancer and The Family

Forward To The Future

August 9, 10, 11, 1996
Sheraton Cavalier Hotel, Calgary, Alberta

Saturday, August 10, 1996

We will participate in the Candlelighters Canada Luncheon for Parent Group Leaders, and Saturday afternoon session:

Treatment of Congenital and Chemotherapy induced Neutropenia

Participating Doctors include:

Dr. Woodman:
- *Neutrophil Function Chronic Granulomatosis*

Dr. Cham
- *Chemotherapy Induced Neutropenia*

Dr. Freedman
- *Congenital Neutropenia*

Introduction:
Lorna Stevens

Saturday evening there will be a Great Western Hoe-down.

All western province & state families *please attend.*

Meal plan & room reduced rates.

Call us for details on our toll-free hotline

Hospital for Sick Children Conference

Toronto, Ontario
Sunday May 26 1:30 PM
Room 6704, 6th Floor

Guest Speaker: Dr. John Doyle

Call our Ontario Chair Shirley Cox 1-705-424-1285 for more information

"It is a very helpless feeling when you don't know what you're dealing with or how to deal with it"

Please join us and network with 20 -30 families.

(Notices were sent out to all Ontario families in early May.)

* * *

Picnic in the Park

Winnipeg, Manitoba

In June, families will be notified by phone with further details.

Lindsey and Lee Stevens at last N.S.A.I. picnic

Neutropenia PSA

The Neutropenia Support Assoc. Inc. now has a Public service announcement.

Here is the script from that tape:

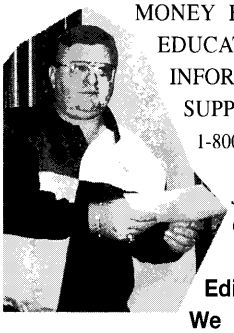
SCRIPT #1

V #1: (FEMALE) IT'S A VERY HELPLESS FEELING WHEN YOU DON'T KNOW WHAT YOU'RE DEALING WITH OR HOW TO DEAL WITH IT!

V #2: (MALE) NEUTROPENIA IS A BLOOD DISORDER YOU DON'T OFTEN HEAR ABOUT, BUT IT CAN AFFECT ANYONE. SOME PEOPLE ARE BORN WITH IT. IT CAN HAPPEN AFTER A VIRAL INFECTION. AND SOMETIMES IT HAPPENS FOR NO KNOWN REASON.

V #1: ALTHOUGH THERE IS A TREATMENT, WE ARE STILL LOOKING FOR A CURE. BUT THANKS TO THE NEUTROPENIA SUPPORT ASSOCIATION WE KNOW WE'RE NOT ALONE.

V #2: THE NEUTROPENIA SUPPORT ASSOCIATION PROVIDES ASSISTANCE TO PATIENTS AND THEIR FAMILIES AND RAISES MONEY FOR RESEARCH AND EDUCATION. FOR MORE INFORMATION OR TO HELP SUPPORT THIS CAUSE CALL 1-800-6 NEUTRO.



Jim Benzelock
CJOB/97.5FM

Editor's note:
We sincerely appreciate the public service announcements provided by CJOB/97.5 FM helping to promote awareness. This PSA is available for use by other stations, so please call for your tape. ■

N.O.R.D.

"We are pleased to inform you that the Neutropenia Support Association, Inc. has been accepted as an Associate Organizational Member of the National Organization for Rare Disorders (NORD).

...You will be receiving copies of our periodic interagency bulletin, ***NORD On-Line***, as well as our newsletter, ***Orphan Disease Update.***"

New Killer Virus on Rise: MD

Re-Print from an article in The Winnipeg Free Press July 11, 1995

Canadian Press
by Deborah McDougall

TORONTO - A killer virus that attacks the human brain could spark another crisis in Canada's blood supply unless urgent action is taken, a federal inquiry was told yesterday.

Dr. Nathan Kobrinsky said a virus called Jacob-Creutzfeld could wreak the same havoc that AIDS caused in the Canadian blood system if scientists don't find a way to detect and deactivate it.

"I hope we're not facing Krever Part TWO a decade from now" said Kobrinsky, staring directly at inquiry head Justice Horace Krever.

His dire warnings came at the end of testimony at the inquiry probing Canada's tainted-blood scandal.

Krever is probing why thousands of Canadians were infected with the AIDS virus and other blood-borne diseases in the 1980s.

But Kobrinsky said that if science doesn't quickly untangle the mysteries surrounding the little-known virus, it could cause another tragedy.

Researchers aren't yet sure exactly how it's transmitted and how many people have died from it so far, he said.

But at least two blood donors in the United States have died from the virus and had their blood recalled, said Kobrinsky, a hematologist at a cancer centre in Fargo, N.D.

He wasn't sure where the donors were from or when the recall happened.

What is known is that the virus is spread through human tissue, said Kobrinsky.

About 10 years ago, it infected several Americans who had been given a growth hormone that originated from ground-up brain tissue taken from cadavers, he said.

The American blood donors who died from the virus had not taken the growth hormone.

Editor's Note:
Dr. Kobrinsky was our 1980's 1st Medical advisor. He was the inspiration for the Neutropenia Support Assoc. Inc. initiative formed in 1989.

Response from Dr. Bonnie Cham

Manitoba Cancer Treatment and Research Foundation

Although the risk of transmission of infection via blood products is very low, it can never be said to be zero. All blood and blood products used in Canada are tested for infectious disease prior to being transfused however there is always the risk of a new "bug" emerging.

Pooled blood products (i.e. one product made from the donations of hundreds of donors) such as IVIG, run the risk of exposure to hundreds of donors with each transfusion. These products are also tested and treated to inactivate all known infectious agents.

Recently however, concern has been raised about the theoretical possibility of transmission of Creutzfeld Jakob Disease (CJD) via blood products. This is a degenerative brain disease whose transmission has been seen in the past with the use of growth hormone derived from human pituitary glands as well as transplants of neurological tissue such as the dura (which covers the brain). There have been no documented cases of this disease being transmitted via blood transfusions. Importantly, those patients who receive frequent transfusions of pooled blood products, such as hemophiliacs, have not been shown to have an increased incidence of this disease. Despite the lack of evidence for blood transmission of CJD, the Canadian Red Cross has been in line with American agencies in developing a policy to recall any product donated from a person who later develops symptoms of CJD. This has been felt to be the safest route to take by both the American and Canadian Red Cross.

As always in medicine, the risks and benefits of any intervention need to be seriously taken into account prior to prescribing any treatment. For patients who require IVIG, or any blood product, if the risks of not receiving the product are significant, and there is no reasonable alternative, then the very slight risk of acquiring an infection must be accepted. All these factors need to be taken into consideration prior to the use of a blood product.

There was an article published in JAMA (Journal of American Medical Association) June 21, 1995, (pp 1865 - 1868) entitled "Recommendations for Off-Label use of Intravenously Administered Immonoglobulin Preparations". There are only 3 licensed indications for IVIG: IPT, immonodeficiency syndromes, and Kawasaki disease.

Ask the Doctors

Dr. Mel Freedman *Dr. Bonnie Cham*

Q: WHat is your opionion regarding the use of IVIG as a treatment for SCN?

A: Intravenous gamma-globulin (IVIG) is successfully use to treat blood disorders in which an immune mechanism is the cause of a low blood count. The classic example of this is ITP (idiopathic thrombocytopenic purpura), in which the patient has a low platelet count due to an immune process. Because of this success, IVIG has been used in the treatment of autoimmune Neutropenia of infancy (seen primarily in young children). Reports of this therapy have shown that some patients may have a short-lived increase in their neutrophil counts, but within days they are generally neutropenic again. Therefore IVIG is not a front line therapy for severe chronic Neutropenia.

Patients with autoimmune Neutropenia of infancy who suffer a significant bacterial infection may benefit from the use of IVIG to temporarily raise their neutrophil count until the infection is under control. Other patients that may benefit are those who have a co-existing immune defect resulting in low immunoglobulin levels. In these patients IVIG is useful as a monthly replacement therapy but not as a therapy for their Neutropenia.

Editor's Note: It could take 20 years or even longer for symptoms of this disease to appear. The Neutropenia Support Association Inc. was first made aware of this potential hazard in 1995 when a family in our network received notification from the Canadian Red Cross that the Gamma Globulins blood product received by their child was potentially tainted with Creutzfeld Jakob Disease. We have now collected numerous articles and can help by sharing this information. See "Ask the Doctors" regarding the use of IVIG as a treatment for SCN.

ACCH Canada Conference

Lorna Stevens participated and represented the Neutropenia Support Assoc. Inc.

REPORT, OF THE
ACCH CANADA CONFERENCE
OCTOBER 28-29TH. 1995

This conference was planned for the purpose of developing a vision and structure for a national organization devoted to the development and implementation of family-centered approaches in pediatric health care in Canada.

The Conference Organizing Committee of the Canadian Issues Task Force planned the ACCH Canada Conference to bring together multidisciplinary participation with a high percentage of parents, representation from all geographic areas of Canada, from organizations involved in child and family health care. The Committee kept total participation at less than 50 in order to maintain effective working communications.

There was a consensus that ACCH Canada would fare best as an independent organization, seeking out affiliations, alliances and cooperative working relationships on projects of mutual interest with a number of other Canadian health care organizations.

ACCH Canada will be a national leader promoting excellence in humanistic, integrated health care to children, youth and families, through the partnership of parents, the volunteer sector, health care professionals including researchers, product and service providers, and policy and decision makers to ensure a positive nurturing environment for the well being and development of children and youth.

The organization should foster collaborative partnerships between all participants in child and family health care. It should work towards integrated health care as opposed to focusing only on the delivery system. It should focus on wellness, maximizing potential, achieving aspirations, healthy families and health communities. It should provide leadership as an organization which is itself, a model of family-centered care and collaborative work. ■

A Strong Plea Goes Out to our Government

To The Honourable Gary Filmon
Legislative Building
Winnipeg, Manitoba
R3C 0V8

Dear Gary;

As volunteer activists, part of the Neutropenia Support Association's mandate relates to education, research, and support. It also involves a continual process to help influence change in a manner which is fair and equitable. No one dealing with a chronic illness wants to be considered as a burden to society.

You have received our correspondence supporting the Manitoba Cancer Treatment and Research Foundation's need for building redevelopment and expansion. The current facility is vastly overcrowded and the radiation therapy waiting lists exceed the recent international standards. Even with all the drastic cuts in Alberta and Ontario, for example, their wait is still maintained at zero. As you are no doubt aware, a seven week wait in Manitoba can have a detrimental impact on the successful outcome of cancer treatment.

Both you and Janice have been part of the building committee board of directors, with Janice as honorary chairperson and yourself as an honorary spokesperson. We understand that $10.5 million has been raised publicly since this project began in 1989. This project was fully endorsed and recognized during the last election campaign as being of top priority. It was decided this project must proceed because of the many issues. These issues include the Community Cancer Program, multi- disciplinary management consisting of a brain tumour clinic, head and neck clinic, surgical oncologists, neurologists, and other specialists integrated into patient care. The increasing workload and crowded facilities has been increasing for many years and we have reached a time sensitive point in the decision making process. We understand the negotiations have been stressed to the limit over a period of years.

A commitment was made and now it is very frustrating for all those concerned with cancer treatment to have to revisit the well documented facts. We also know, that for Manitoba to recruit and retain quality cancer specialists it has been difficult. Last year only 12 oncologists received their certification in all of Canada. The demand for cancer treatment is felt in all provinces and most provinces are in the process of adding space for additional radio therapy units to respond to increasing workloads. The University of Manitoba Cell Biology research scientists are also part of the integrated team and the scope of their present programs is challenged by your decision to suspend their much needed space. These same research scientists are also clinicians serving the needs of cancer patients, rare blood diseases like Neutropenia, and other infectious and chronic illness present at Children's Hospital.

We know the site has been determined by the advisory boards and design teams so we find it difficult to understand why the funding has been cut off. We want Manitobans to have quality and affordable healthcare and the best way to meet this goal is through the careful spending of the healthcare dollars that are available. In our opinion, a government is elected to priorize and make choices wisely, ensuring common sense decisions are made for the long term well being of Manitobans.

There is no question that a great deal of money is being spent in Manitoba and your recently released Manitoba Fact Health Sheet supports this. Transfer payments are $50 million higher than when the election go ahead was reconfirmed. The MHO services which are now being handled by Comcheq, I.S.M. (IBM subsidiary) proposed nursing resource centres, midwifery plans, obstetrics down sizing, reduction in pharmacare costs, as well as other planned initiatives support the position that we are in better financial shape now than in previous years.

In summary, we hope to hear from you in the near future regarding these pressing issues. The MCTRF investment in Manitobans' future needs to go forward. ■

The Honourable Jim McCrae
Minister of Health
302 Legislative Building
Winnipeg, MB R3C 0V8
Telephone: 945-5126
Fax: 945-0441

Dear Mr. McCrae:

We wish to express our deep concern regarding the decision of government to suspend the redevelopment and expansion of cancer facilities for the Manitoba Cancer Treatment and Research Foundation at 100 Olivia Street.

The Cancer Foundation is extremely crowded. The chemotherapy facilities are regularly overcrowded and are supporting many more patients than can be treated in a safe, efficient and comfortable manner. On children's days, the halls are filled with children on treatment, waiting adults and family members. The waiting area for the laboratory is in the main hallway of the cancer center.

There are long waiting lists for radiation therapy. Additional machines and staff are required. There are few private spaces to speak with the nurses or doctors. This center does not meet today's needs and certainly will not meet the needs of tomorrow. The quality of cancer care being delivered to patients will be compromised without new facilities.

We ask you to immediately reverse this decision and give the Cancer Foundation approval to proceed with planning and construction of an expansion of the present facility.

Sincerely yours,

_____
Name

_____
Address

_____
Telephone

cc: Your MLA

Editor's Note: Please help us by sending this letter

Editor's Info Tidbits

Herbal remedies

Herbalism, originating from traditional Chinese medicine is an ancient form of treatment using plants and animal extracts, often In pill form Some of our most widely used modern drugs originate from plants although the healing substances are now often chemically synthesized. Herbal remedies are available in health food shops, traditional ethnic stores, naturopaths and herbalists. In Canada most herbal products are not legally permitted to be sold as medication, but only as foods, and warning labels are therefore not required. While most herbs are harmless when used in moderation, large doses can cause adverse reactions, for example, bleeding, gastrointestinal problems and liver disorders have been associated with strong herbal teas such as comfrey and gordolobos.

Tips on using herbal remedies

- always tell your doctor what herbs you are taking
- use herbal products only in moderation and for short periods
- do not give children under two years of age herbal teas
- be cautious using very concentrated oils and teas
- purchase herbs only from established and reputable source
- ask about what you are buying, the dose, Latin name, and uses

Editor's Note:
Many have inquired about accupuncture. This may be *extremely dangerous*. When dealing with chronic illness you may in desperation seek alternatives. Please understand the treament of this disorder is complicated. Your child needs the long-term assistance of specialists. This is another reason why the Neutropenia Registry is so valuable to you as caregivers. You will then be in the "loop" and be informed about all helpful disease management aspects.

Physician Research News

The Hanover Team!

"Neupogen (G-CSF) is known to act on developing neutrophils via proteins on the surface of these cells known as receptors. Following attachment of G-CSF to the receptor, a message is sent into the cell to stimulate neutrophil production. It has been shown in the past that patients with congenital Neutropenia (Kostmann's syndrome) have normal to elevated levels of G-CSF and it has been thought therefore that there may be a problem with either the structure of the receptor protein on the neutrophil surface or with the signal which the receptor sends into the cell once the G-CSF attaches itself to the receptor (binds). Two interesting papers presented at the ASH meeting (American Society of Hematology) looked at the structure of both the receptor and the gene which codes for the receptor

The ASH Papers By Touw and Kasper

Touw and his group in Rotterdam, collaborated with the Severe Chronic Neutropenia International Registry (SCNIR) to analyze the structure (DNA sequence) of the receptor gene in 25 patients with congenital Neutropenia. They found 5 of the 25 patients who had abnormalities in the DNA sequence of the receptor gene. This abnormality was found only in the cells of myeloid lineage (i.e. early neutrophil cells). This indicates that the abnormality expect to find it in all cells of the body, but rather one which developed over time. Three of these five patients developed cytogenetic abnormalities (abnormalities in the chromosomes of the bone marrow cells) and went on to develop leukemia. Of the other two, one has developed a chromosomal abnormality. These findings support the idea that abnormalities developing in the G-CSF receptor gene are associated with progression from Severe Chronic Neutropenia (SCN) to leukemia and may be an early marker of this development.

Kasper and his research group from Hannover, looked at the actual receptor protein structure (rather than the structure of the gene which codes for the protein as looked at by Touw). In patients with SCN the receptor was found to be the same size as in normal controls , indicating that the structure of the receptor is not likely to be the problem in SCN patients. Further exciting work is being done in various labs looking at the signal which the receptor sends into the cell once it binds to G-CSF to determine where the problem actually is in Kostmann's syndrome.

Reviewed by Canadian SCN International Registry Physician..
Bonnie Cham, MD, FRCPC
Assistant Professor
Dept. of Pediatrics
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E-Mail - Bonnie@mctrf.mb.ca
Address Manitoba Cancer Treatment and Research Foundation
ON 141-100 Olivia St.
Winnipeg, Manitoba
R3E 0V9

Editor's Note:
The Neutropenia Support Assoc. Inc. wishes to acknowledge the efforts of Dr. Bonnie Cham. She has helped with the "medicalese" by summarizing these important research papers presented at the A.S.H. Conference Dec. 1995, Seattle, Washington. The Neutropenia related research underway is EXTRAORDINARY! The research continues to help answer many questions for us all. Should you wish your donation 100% be given to research, please earmark your cheque accordingly. Thank-You! ■

Letter from Dr. Cory

G-CSF (Neupogen) has been a miracle drug in stimulating neutrophil production and preventing life-threatening infections in children with severe congenital Neutropenia. In a few well-documented cases, loss of a chromosome has occurred after administration of G-CSF. This is associated with a pre-leukemia condition. Although children with SCN had an increased incidence of leukemia before G-CSF was available, the issue of G-CSF's contributing to leukemia development has been brought up.

We have been interested in the mechanisms whereby precursors of neutrophils proliferate and mature. In particular, we want to know which proteins associated with tyrosine kinases (enzymes that control growth and development) are necessary for G-CSF-stimulated proliferation and maturation. We hypothesize that some forms of SCN may be due to defects in these proteins. We also hypothesize that some of these defective proteins contribute to the development of leukemia - with or without G-CSF. A practical application of these studies is to better identify patients at risk for leukemia and to intervene at an earlier stage.

The American Cancer Society has approved for funding our project to answer some of these questions. We will be studying at the genetic and protein levels the effects of G-CSF on white cell maturation. Because SCN is a rare disease, we will also create an animal model to test our hypothesis of the role of growth factors on leukemia.

We welcome heparinized bone marrow samples (1-2 cc) from children with SCN at time of diagnosis, at intervals, and at time of suspected bone marrow changes.

Thank you

Seth Corey. MD MPH
Assistant Professor of Pediatrics and Pharmacology
University of Pittsburgh
Children's Hospital of Pittsburgh

Refer to paper Ash 1691, A.L Kindzelskii, M.M. Eszes, R.F. Todd III and H.R. Petty, Review kindly prepared by:

A. L. Kindzelskii, MD, Ph. D.
Department of Bio. Sciences
Wayne State University
410 W. Warren Ave.
Detroit, MI. 48202, USA

Leukocyte transmigration into tissue is a key role in the inate immune system. In order for cells such as neutrophils to perform effector functions in the first line defense against infection, the cells must first be able to leave circulation and enter the tissue, The process of cell adherence to endothelial cells involves a battery of receptors beginning with selectins and ending with tight adherence to the endothelial walls by integrins. Once the cell has adhered to the endothelium, a process of migration and the eventual escape of the neutrophil through the endothelial layer and basement membrane allows the neutrophil to enter the tissue.

The process of diapedesis involves both the tight adherence of the neutrophil as well as the clearance of a path between adjacent endothelial cells. Tight adherence to the endothelium is mediated through integrins such as CR3 (CD11b/CD18;(m(2;Mac-1). The stimulation of Proteolytic enzymes can be achieved through molecules such as the urokinase plasminogen activator receptor which cleaves plasminogen to plasmin. In this study we have shown an interaction between known adherence integrins CR3 and CR4 (CD11c/CD18;(x(2;pl50,95) with a receptor for the urokinase-type plasminogen activator (uPAR;CD87). This interaction very may well hint to a functional relationship between membrane receptors in mediating cellular events corresponding to the constituitive metabolic pathways and the induced activation associated with phosphorylation patterns and the stimulation of the glycolytic cycle.

Cell migration is a key feature of host defense. It employs regular cycles of cell attachment and release. The (2 integrins of leukocytes play a key role in their adherence to other cells, the extracellular matrix, and other surfaces while urokinase-type plasminogen activator receptors, or uPAR, promote localized uPA-mediated proteolysis.

Recent work in our laboratory has shown that certain GPI-linked receptors, including uPAR, are physically associated with CR3 in neutrophil membranes. These GPI-linked receptors may utilize the signal transduction apparatus of CR3 to mediate certain signal transduction events. Previous studies have also shown that physical associations between uPAR and CR3 are severed as cells polarize for locomotion: uPAR accumulates at the lamellipodium of a polarized cell while CR3 traffics to the uropod.

Dr. Kindzelskii and Lorna Stevens at A.S.H.

We now show that CR4 also accumulates at the lamellipodium of polarized neutrophils. We hypothesize that CR4 may restrain uPAR at the lamellipodium. Using optical microscopic and resonance energy transfer techniques we have found that CR4 and uPAR are in close physical proximity on migrating, but not stationary, neutrophils. Furthermore, we have discovered that these interactions are oscillatory, thus suggesting novel features of the signal transduction system during cell motility. Preliminary data suggest that these oscillations are driven by metabolic clocks.

To assess the time-dependent cell surface distribution of CR3, CR4 and uPAR, neutrophils were labeled with Fab or F(ab')2 fragments of monoclonal antibodies directed against these molecules, each conjugated with a different fluorescent chromophore. This makes it possible to visualize the location of all three receptors on the same cell.

Imaging experiments can show that CR4 and uPAR co-localize to the same membrane domain, but do not provide information regarding their physical proximity at the molecular level. Thus, RET experiments were performed. CR4 and uPAR were labeled with Fab or F(ab')2 fragments of corresponding antibodies, conjugated to donor (FITC) or acceptor (TRITC) chromophores. The intensity of the RET emission channel was measured by using a photon counting apparatus, and

(continued next page)

The Neutropenia Support Association Inc.
has gratefully received
many "In Memory of" donations.
May the knowledge that this gift will aid others be of comfort.
The families have received acknowledgements of the generous donations.
We continue our efforts with help from your tax deductible donations.

Thank You!

was greatly increased on polarized cells. However, the RET intensity did not reach a stable plateau, but rather oscillated at a constant frequency. The oscillating RET level of cells undergoing spontaneous locomotion shows rhythmic coupling approximating a sine wave with a 22 sec. period. These oscillations cannot be due to some instrumental artifact since they disappear when cells return to a spherical morphology. They are absent on fixed cells or in experiments were RET was mesured between uPAR or CR3 and other plasma membrane components such as Mo5 or fluorescent lipid analogues.

We first hypothesized that the RET intensity oscillations are coupled to signal transduction pathways. To explore this possibility we measured the RET channel output of CR$ and uPAR labeled neutrophils during migration on various surfaces and in presence of different biologically active compounds. Fibrinogen coated glass surfaces increased the oscillation period to 13 sec. in the form of a sine wave. Similar CR4-uPAR interactions were found on neutrophils migrating upon endothelial cells grown in vitro. The amplitude and frequency of the RET channel emission were both reduced by exposure to 100uM indomethacin while migrating on endothelial cell monolayers.

To further test the role of signal transduction cascades in interreceptor oscillations, the chemotactic factor N-formyl-met-leuphe (FMLP) was used. At a concentration of 10-7 M , it was also found to increase the frequency of CR4's oscillatory behavior.

Since (2 integrins are known to be regulated by phosphorylation of their (chain, we tested the potential roles of phosphorylation reactions. Staurosporine, a kinase inhibitor, in sub-optimal doses, changed the sine wave oscillations of CR4-uPAR proximity into a flyback sawtooth waveform. Conversely, the addition of 50uM pervanadate led to a reverse sawtooth (negative going ramp) of increased frequency.

We next hypothesized that the ocillatory signal transduction apparatus was driven by metabolic clocks. Therefore, we examined oscillations in the NADH/NADPH concentration by monitoring their autofluorescence intensity. Stationary neutrophils exhibited sinusoidal NADH autofluorescence oscillations with a period of roughly 3 minutes. However, migrating cells demonstrated a sinusoidal 20 second oscillation in addition to the longer 3 minute oscillation. The periods of rapid metabolic oscillations were identically sensitive to the same conditions or factors tested above in the CR4/uPAR energy transfer experiments.

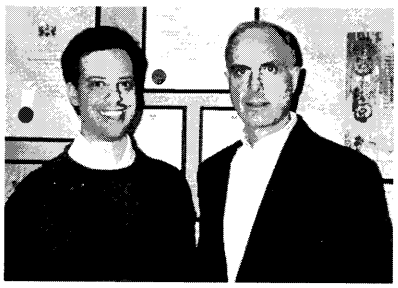
To determine the phase relationships between RET and NADH oscillations, we performed experiments wherein both the CR4-uPAR RET channel intensity and NADH autofluorescence intensity of migrating neutrophils were monitored. These data showed that CR4uPAR RET and NADH autofluorescence have the same frequency but are 180(out of phase. This result is not surprising considering that NADH and ATP oscillations are 180(out of phase. However, the NADPH waveforms were all apparently sinusoidal, suggesting that waveform modulation is downstream from glycolytic oscillations.

Previous workers have detected regular oscillations in neutrophil: shape change, actin assembly, and respiratory burst. Our findings suggest a model of neutrophil migration wherein CR4 molecules at the lamellipodium are simultaneously phosphorylated by phase-lock signaling machinery, which leads to CR4-to-uPAR coupling and focuses proteolysis next to the region where cell extension is to occur. Cell extension and actin assembly then proceed through this site of adherence/proteolysis.

In conclusion we want to underline a few points of this work. First, the locations of the integrins CR3 and CR4 correlate with the axis of neutrophil migration. Second, this provides the first evidence of oscillatory interactions between two membrane receptors and signal transduction phase-locking. The relationships between these receptor interactions and metabolic oscillations suggest that these measures reflect the same general machinery, which is regulated by "internal metabolic clock". All of these cellular phenomena may thus be coordinated at the molecular level; the result of which is a physiolocal response in which cell adherence, focused proteolysis, actin assembly and shape change are all properly timed to yield temporally coordinated events. ■

Dr. Freedman's Lab

Novel treatment concept blocks signals that control growth of leukemia cells



Dr. Mel Freedman and son Dr.Jamie Freedman presented papers at the A.S.H. conference.

TORONTO - Researchers at Toronto's Hospital for Sick Children (HSC) have developed a novel concept for anti-cancer treatment of recurrent acute lymphoblastic leukemia, the most common form of childhood cancer. Their approach is to selectively block an intracellular transmitter of signals which control the growth of leukemia cells,

Researchers have demonstrated - for the first time - that the enzyme Jak-2, which acts as a transmitter of cell growth signals, is overabundant and abnormally active in recurrent leukemia cells. This causes the leukemia cells to reproduce uncontrollably.

Dr. Roifman and colleagues screened a variety of compounds in Dr. Mel Freedman's lab which have the potential to block the activity of Jak-2. They discovered that the compound AG-490 inhibited the function of Jak-2 but not other enzymes and killed leukemia cells in vitro. (The compounds were prepared by collaborators Drs. Alexander Levitzki and Aviv Gazit of the Hebrew University, Jerusalem.)

"'We also found that AG-490 was effective in eliminating leukemia growth in immunodeficient mice which had been transplanted with human leukemia cells " a leukemic cell line established by Dr. Freedman from a patient in his hematology clinic. Dr. Roifman explains. "The AG-490 had no adverse effect on their normal blood system, indicating that this compound is also very effective in vivo."

In acute lymphoblastic leukemia, an excessive number of abnormal immature white blood cells (called blasts) are produced in the bone marrow. These immature cells are driven by growth factors and their receptors which are expressed in leukemia. Central to transmission of cell growth signals through such receptors are a family of enzymes, including Jak-2. ■

From The Mail Room

We were very happy to receive the information on the National Registry that had been setup....

***

I can't say enough praise for doctors ..... who helped us immensely ... and pointed us in the direction of this support group. The publications have been very informative and supportive and provides an avenue to learn more information and just relate to other families in the same situation

***

I found some of the articles, particularly the article written by Dr. Freedman on Glycogen Storage Disease Type IB to be very interesting.

***

I can't thank you enough for your tireless work in providing an information highway for Neutropenia families and doctors. It is a very helpless feeling when you don't know what you're dealing with or how to deal with it.

***

Thank you from Children's Hospital

I am writing to inform you of the immediate transfer of $1,700 from the Health Sciences Centre Library Services to the Children's Hospital Family Information Library. This money is the remaining portion of donated funds which The Neutropenia Association so generously gave to the Health Sciences Centre Library Services.

These monies will be used to purchase materials regarding Neutropenia, Chemotherapy-induced Neutropenia, and other resources/educational materials related to helping families cope when their children are ill.

The Family Information Library at Children's Hospital operates solely on gifts and grants, and this donation will allow us to purchase materials that will benefit many families.

Mrs. Dianne Cooper
243-A Main Street
Point Leamington, Newfoundland
AON 1Z0

September 13 1995

Dear Mrs. Cooper:

I am pleased to inform you that you have been selected to receive a Canada Volunteer Award Certificate of Merit.

This certificate is awarded each year to recognize those who have made valuable voluntary contributions towards improving the health and social well-being of their fellow citizens.

On behalf of all Canadians, please accept my sincere congratulations.

Diane Marleau
Minister of Health

Editor's Note:
Dianne Cooper is the Chair of the Maritimes Chapter and can be reached at 1-709-484-3592. All of us from the Neutropenia Support Assoc. Inc send our sincere congratulations to Dianne.

And a Big Hardy Well Done Gang!!

Dianne was nominated by Lorna Stevens, a recipient of this award in 1993.

From Students in First Year Dental Hygiene at the University of Manitoba.

As part of our training at the School of Dental Hygiene, we had the privilege of interviewing Lorna Stevens in regards to the Neutropenia society and the work she does with this association. Initially, we knew next to nothing about the condition except that it was a form of blood disorder. Lorna exposed us to every aspect of the condition and we in turn were able to present her touching story along with others to members of our class in a 45 minute presentation. We were stunned to learn the extent of the impact caused by Neutropenia as it can affect every aspect of life for those involved including their families. With this new found understanding, new realizations surfaced. Suddenly, it became crystal clear. It is vital that the health care community establishes interdisciplinary networks so that all information can be interchanged and the knowledge base extended. From issuing a newsletter to lobbying to merely providing support, it is remarkable how much this association has done. Even so, the Neutropenia Support Association still forges ahead in an attempt to educate and inform. In doing so, it has encapsulated the attention of not only us, as students, but our instructors as well. As aspiring hygienists, we felt that we could really be of assistance to those coping with this condition. The oral implications of Neutropenia are extensive and staggering; a fact that we felt obligated to share with both our colleagues and the public. As Lorna stressed, "education is the key issue", and as future members of the hygiene profession, we are willing to assist in any way possible. Thank you once again to Lorna Stevens for her time, the opportunity, and the knowledge she passed along to us as we strove to learn more about Neutropenia. ■

Ask the Doctors

Dr. Mel Freedman *Dr. Bonnie Cham*

Q: What denotes congenital Kostmann ?

A: Cyclics are mostly " congenital" because they present in early life and can also have a clear-cut inheritance pattern... but we are still using the term "congenital" to denote non-cyclic patients that have Neutropenia onset from infancy. When there are 2 or more cases in the same family inheritance is implied, and they are called Kostmann. Some doctors use Kostmann and congenital interchangeably but Kostmann only describes family cases, not sporadic ones.

Q: Regarding the risk of leukemia and the recommendation for cytogenetic studies (bone marrows yearly or every 2 years)?

A: "Prior to the availability of the hematopoietic growth factors (such as Neupogen) it was recognized that patients with congenital Neutropenia and aplastic anemia were at risk of developing leukemia. Based on this knowledge and the concern that there may be some risk associated with long term stimulation of the marrow, regular bone marrow examinations have been done in patients on long term G-CSF. In one group of patients, the patients with congenital Neutropenia (also known as Kostmann's Neutropenia), there have been 12 cases of acute myelogenous leukemia (AML) and one case of myelodysplastic (MDS) in a total of 184 patients up to December 31, 1994. Nine of these patients had a chromosomal abnormality (monosomy 7)in their bone marrow detected by cytogenetic studies (examination of chromosomes) which developed after an average of 54 months of G-CSF therapy. In several of these cases, this occurred before the development of leukemia. The regular bone marrow examinations and cytogenetics studies have allowed us to recognize and investigate the step in evolution to MDS or AML in congenital Neutropenia and the opportunity to understand better why these changes occur.

To date all leukemic conversions have occurred in the congenital Neutropenia group. At present the rate for patients with idiopathic and cyclic Neutropenia remains at 0%. For patients with congenital Neutropenia, the incidence rate is approximately 5% at 5 years of therapy; the rate before the use of G-CSF is not known. There have not been enough patients treated for longer than 5 years to predict what will happen as length of treatment increases. It is unclear what relationship there is between the development of leukemia and the G-CSF therapy .

We would therefore strongly recommend that annual bone marrow exams with cytogenetics be performed on these patients in order to increase our knowledge regarding the evolution of these changes, as well as to potentially diagnose these conditions in the early pre-symptomatic stages."

Q: Should Ear Piercing be performed on a patient with Neutropenia ?

A: If the neutrophil number is 1000 or better there is no problem but the job should be done by a pro with great attention at the time and during healing to local hygeine. Between 500 and 1000 is moderately safe also, but not as safe, closer to 1000 is more of a comfort zone than closer to 500. Under 500 , it is not advisable. ■

Recommended Reading!

Neutropenia Causes, Consequences and Care

Normalization of Intracellular Calcium: A sweet Solution to Neutrophil Dysfunction in Diabetes?

Annals of Internal Medicine Volume 123 Number 12 December 15, 1995 Page 952..

Polymorphonuclear Leukocytes in Non-Insulin-Dependent Diabetes Mellitus: Abnormalities in Metabolism and Function

Annals of Internal Medicine Volume 123 Number 12 December 15, 1995 Page 919..

Periodontal Disease in Three Siblings With Familial Neutropenia

J Periodontol 1993; 64:566-570 ..June 1993

Chemotherapy and Neutropenia: Information for persons and their families.

Booklet explains causes and basis of neutropenia, fevers and infections and provides practical suggestions for dealing with Neutropenia when it occurs. Produced by the Neutropenia Support Association and Sponsored by Amgen Canada. Price: No charge. English and French available.

The Candlelighters Guide to Bone Marrow Transplants in Children.

An excellent collection of articles by parents and professionals dealing with the many aspects of bone marrow transplants. It is designed to help parents make informed decisions and to gain some sense of control. Edited by F. Leonard Johnston and Ellen I. O'Donnell. Published by U.S. Candlelighters, 1993. This book is made available through a generous donation from the U.S. Candlelighters. Price: no charge for parents.

EMLA Colouring Book: A Fun and Games Book to Make You Smile

A colouring book for the preschool and early school age children designed to help them learn how the proper application of EMLA can prevent the pain of invasive procedures. Includes games to help pass the time while waiting. Produced by Astra Pharma. Price: No Charge.

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SCN Registry in Canada

Registration is facilitated by the two Canadian registry physician contacts, Dr. Melvin Freedman, Toronto Sick Children's Hospital (ph: 416-813-6152 fax: 416-813-5327), and Dr. Bonnie Cham, Manitoba Cancer Treatment & Research Foundation (ph: 204-787-2188, fax: 204-783-6875).

Registration forms will be provided to the referring physician. Information on reimbursement possibilities will be outlined by Dr. Freedman and Dr. Cham.

INFORMATION ORDER FORM

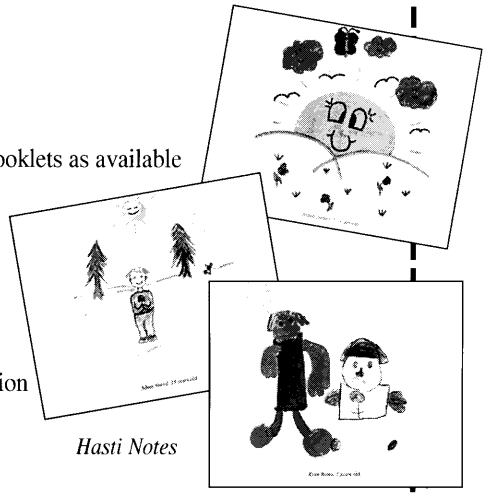
SEND TO:

THE NEUTROPENIA SUPPORT ASSOCIATION INC.

P.O. BOX 243, 905 CORYDON AVENUE, WINNIPEG, MANITOBA, CANADA R3M 3S7
TELEPHONE: (IN WINNIPEG) 489-8454 OR (CANADAWIDE) 1-800-663-8876

Please Forward:

_____ (for young children) "Sammy the Syringe", "Marvin's Marvelous Medicine", and other booklets as available
_____ copies of "Neutropenia - Causes, Consequences and Care" (English)
_____ copies of "Neutropenia - Causes, Consequences and Care" (French)
_____ copies of the Neutropenia Support Association Newsletter and back issues (as available)
_____ copies of Chemotherapy and Neutropenia (English)
_____ copies of Chemotherapy and Neutropenia (French)
_____ Video tape — Physician Presentations
_____ Video tape — Physician presentations "in layman's terms" and N.S.A.I. general information
_____ Update mailing information only
_____ "Caring Cards" Hasti Notes #_____ (6 for $5.00) Cheque only, enclosed.



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