Volume 9 Winter 1997

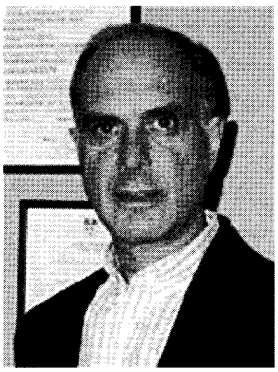
"Giving is Rewarding" Neutropenia News Network

Neutropenia Support Assoc. Inc.

P.O. Box 243, 905 Corydon Ave. Winnipeg, Manitoba R3M 3S7
Local Winnipeg (204) 489-8454 Toll Free # 1-800-6-neutro (1-800-663-8876)

President: Lorna Stevens (204) 989-5000 E-mail: STEVENSL@NEUTROPENIA.CA Directors: Janis and Jim Benzelock
Vice President/Editor: Mike Carlson E-mail: CARLSONM@neutropenia.ca Treasurer: W. Lorne Stevens Legal Advisor: R. Stefanyshyn
Canadian SCN Disease Registry: Dr. Bonnie Cham Dr. Melvin Freedman

Sound Advice From The Experts



Dr. Melvin Freedman

For patients with severe chronic Neutropenia, their families, and treating Physicians:

The Severe Chronic Neutropenia International Registry (SCNIR) meets regularly to monitor disease and treatment outcomes of patients with various forms of severe chronic Neutropenia (SCN). The SCNIR has a large database with long term information on more than 500 patients. Using this valuable material, the SCNIR and its Sub-committee on Safety have been able to make recommendations to patients, their families and their treating physicians about the administration of G-CSF (Neupogen) and about the monitoring of bone marrow function. The following two recommendations are in effect for 1997 and 1998.

Annual Bone Marrow Evaluation

Approximately 10% of SCN patients with the congenital or Kostmann's form of Neutropenia have developed myelodysplastic syndrome (MDS) and/or acute myeloblastic leukemia (AML). SCNIR research studies have shown that marrow cells of patients who have developed MDS/AML have also showed chromosome abnormalities and other cellular changes indicative of the malignant transformation. Using this knowledge, the SCNIR recommends that all patients with congenital or Kostmann's Neutropenia receiving G-CSF have an annual bone marrow evaluation for microscopic inspection of the specimen, and for chromosome and possibly other studies that may identify those patients early who are at risk of MDS/AML. This recommendation also applies to patients with Shwachman-Diamond syndrome because of their predisposition to MDS/AML. Early detection will allow the initiation of a treatment plan before overt disease, which is more difficult to manage, becomes manifested.

Since MDS/AML has not yet been seen in SCN patients with glycogen storage disease type Ib., with cyclic Neutropenia, or with idiopathic forms of Neutropenia, annual bone marrow testing for these patients can be waived at the discretion of physician and patient, but careful, serial monitoring of blood counts and physical status should continue.

The Need to Continue G-CSF Treatment

G-CSF treatment of SCN patients is highly effective in more than 90% of cases and induces the production of neutrophils to levels that prevent infection and related complications. For congenital and Kostmann's Neutropenia and for cyclic Neutropenia, G-CSF doses and scheduling of administration may vary somewhat from patient to patient. But G-CSF cannot be stopped. Discontinuing G-CSF therapy in these patients inevitably leads to recurrence of severe Neutropenia. Until an equally effective substitute product or alternative treatment becomes available, the SCNIR currently believes that G-CSF therapy in these patients is for the long-term.

Similarly, most patients with idiopathic Neutropenia require long-term G-CSF therapy. However, there may be small numbers of patients in this subgroup who spontaneously have an improvement in neutrophil numbers and will not require continuous G-CSF therapy. This will only happen in a minority of cases and must be determined by the treating physician on a case-by-case basis.

Submitted by
Dr. Melvin H. Freedman
Severe Chronic Neutropenia
International Registry

From the Research Lab of Dr. Melvin H. Freedman

The Hospital for Sick Children
Division of Haematology/oncology

My focus now is on Shwachman syndrome. Basically this is Neutropenia with faulty intestinal absorption because of pancreatic insufficiency. It's inherited; mom and dad pass on the genes to offspring. The double dose of faulty genes produces the syndrome. The Neutropenia can be severe and require G-CSF. The marrow failure can be more generalized. There is a 10-30% incidence of AML/MDS even in patients not treated with G-CSF. Thus, this is anther pre-leukemic disorder. I am now re-calling a large number of patients for annual marrow assessments to answer research questions about what the fundamental marrow problem really is and if we can identify the sub-group that will get leukemia.

Obviously this has great implications for patients and families, especially those patients that need G-CSF. The marrows will be tested for chromosome changes, and assayed in cell cultures for the numbers of blood-forming precursors and for the ability of patient and normal donors' marrow supportive structural cells (called stroma) to support the blood-forming ability of patient and normal stem cells (called CD34+ cells). We will also assess the number of G-CSF receptors on granulocytic cells and the binding of G-CSF to the receptors. Finally, we will look for mutations in the ras oncogene and in G-CSF receptors. These studies are expensive and we are having difficulty funding the research. I approached the Shwachman group in the US but they don't have sufficient uncommitted resources currently for this type of research. My guess is that this big study for about 25 patients will run close to $50,000/year to cover technician time and all of the necessary supplies and equipment. The families want these studies!! The research is certain to generate new and important info about Shwachman's. I can get started with your generous "start-up" offer but to do all of the patients will require a solid financial base. Thanks for your ongoing support. I genuinely appreciate your efforts.

Editors note: In 1997 The Neutropenia Support Assoc. has contributed $11,500 to his research, and we hope to raise considerably more to aide in this critical life saving project.

Hematopoietic Growth Factors and Their Receptors in Congenital Bone Marrow Failure

Patients with congenital bone marrow failure have defective hematopoiesis, which is evident early in life. The faulty marrow function varies from single lineage cytopenia to full-blown trilineage aplastic anemia. Since growth and differentiation of bone marrow progenitor cells are controlled by stage and lineage specific growth factors, we hypothesize that in a proportion of patients with congenital bone marrow failure disorders, the defect in hematopoiesis is due to a mutation in a gene coding for either a specific growth factor or its receptor. According to this hypothesis, a defect in a gene coding for a growth factor receptor will manifest itself as unresponsiveness of hematopoietic progenitor cells to that particular growth factor. In contrast, a mutation in a gene coding for a growth factor produced by T-cells or stromal cells may result in an inability of bone marrow stroma or T-cells to sustain hematopoietic colonies in vitro. In this way an assessment of the effects of growth factors on hematopoietic colony growth will provide an initial indication of the locus of a mutation in a particular patient. We propose to test this hypothesis initially by determination of the expression (by internally controlled PCR and flow cytometry), and function (by clonogenic assays) of hematopoietic growth factors and their receptors in cells from patients with bone marrow failure. The results from these experiments will provide the basis for a more direct determination of the expression of a particular growth factor or its receptor followed by the identification of a structural mutation in the specific gene. The following specific aims will be addressed.

(1) To assess the ability of bone marrow cells from patients with congenital bone marrow failure to form hematopoietic colonies and to respond to growth factors. To assess the ability of long term stromal cell cultures from patients with congenital bone marrow failure to support normal hematopoiesis in vitro. To compare the expression of growth factor receptors on bone marrow cells from normal subjects and from patients with congenital bone marrow failure. And to compare the expression of growth factors by cultured bone marrow stromal cells and by activated T lymphocytes from normal subjects and from patients with congenital bone marrow failure.

(2) To identify mutations in candidate genes coding for growth factors or their receptors in selected patients with bone marrow failure. Within the classification of the congenital bone w failure disorders, there is a category called severe congenital Neutropenia. Because of severe impairment in neutrophil production, these, patients develop life-threatening infections. Although the molecular explanation for congenital Neutropenia is not yet known, recombinant granulocyte-colony stimulating factor (G-CSF) overrides the defect when administered clinically and reverses the Neutropenia in patients. In the era prior to G-CSF therapy, there were 2 published cases of congenital Neutropenia evolving into acute myeloid leukemia. Since the widespread use of G-CSF for congenital Neutropenia in the past 5 years, there has been an alarming increase in patients with myelodysplastic syndrome and acute myeloid leukemia. Many of these patients manifest ras oncogene mutations and

monosomy 7 in bone marrow cells, and a few have a mutated G-CSF receptor (G-CSF-R). We hypothesize, therefore, that congenital Neutropenia is associated with a genetic predisposition to myelodysplasia/acute myeloid leukemia and that a subgroup can be identified during its multistep pathogenesis by demonstrating specific genetic aberrations. We also hypothesize that G-CSF therapy accelerates the evolution of myelodysplasia/acute myeloid leukemia.

Thus, the specific aims are

(3) To study by routine cytogenetics and by florescent in situ hybridization patients' cells prior to and during G-CSF therapy with regard to loss of pan or all of chromosome 7. To also look for cytogenetically undetectable lesions on chromosome 7 by analyzing sequence polymorphisms by PCR. To detect ras mutations pre and during G-CSF therapy by SSCP, by allele specific restriction enzyme digests, and by cloning and sequencing mutant ras fragments. And to sequence the cytoplasmic domain of the G-CSF-R in marrow cells at diagnosis, during GCSF therapy and at presentation of leukemia.

(4) To use an in vivo SCID mouse model to test the potential of G-CSF at inducing genetic aberrations in patients' marrow or for selecting genetically unstable marrow cells with these aberrations (ras mutations, monosomy 7, G-CSF-R mutations). Also, in collaboration with others, to identify the signaling partners for the distal differentiation domain of the G-CSF-R in patients, and to analyze the G-CSF/ras pathway in patients' granulocytes (induced to mature with G-CSF) and in normals.

These studies are certain to provide new and important information. Identification of the molecular defects leading to bone marrow failure will lead to a better understanding of the role of hematopoietic growth factors in normals and in bone marrow failure. In the subgroup of patients with congenital Neutropenia, there is growing concern about malignant transformation while receiving G-CSF therapy. This is the first proposal to address this issue in a comprehensive manner.

Update from Dr. Freedman October 10, 1997

It's a bit early to give specifics about the Shwachman-Diamond syndrome initiative except to say that we have already recalled many Canadian patients for detailed hematological assessment and bone marrow research studies. Some of the marrow studies take 4 months to complete; other studies give immediate results. The data unfold like a jigsaw in bits and pieces and we're starting to see important patterns among the patients. We should have some tangible new information by December about the bone marrow function in the syndrome and hopefully ways to detect occult leukemia early which will allow the prompt implementation of a management plan.

A word from Dr. Freedman

Because of the high risk of myelodysplastic syndromes/acute myclogenous leukemia in congenital forms of Neutropenia including Shwachman-Diamond syndrome, I am calling in all of the patients in our area for annual marrow assessments. This is clearly an important opportunity to answer basic questions about the marrow dysfunction that causes Neutropenia in these various syndromes as well as the propensity for developing malignant transformation.

In preparation for such a large commitment, I have developed the following detailed protocol for studying the patients' marrow specimens. There are two goals: To determine the basis for defective marrow function; and, to see if the subgroup that develops leukemia can be identified prior to overt transformation.

With the permission from the patients and families, marrow specimens will be collected under sedation and will be used for:

- chromosome studies to detect early leukemia
- assays in tissue culture of all of the blood forming progenitor cells
- assays for leukemic blast progenitors and stem cells
- chromosome studies on any blast cells that can be identified in these assays
- receptor analysis for the growth factor, G-CSF, by flow cytometry and with radio-labelled cytokine
- long-term tissue cultures of bone marrow structural (stromal) cells to compare potential of patient and normal specimens to support blood forming elements of patient and normal stem cells (CD34+)
- genetic mutations in the ras oncogene that would signify malignant change
- genetic mutations in the G-CSF receptor
- cryopreservation of cells for retrospective studies by qualified investigators

These studies are labour intensive and costly but are certain to provide new information about the neutropenic disorders. My fervent hope is that we can help families directly with new information and to advance the field. These studies are extremely costly and I am extremely grateful for your interest and support.

Sincerely,

Melvin H. Freedman, M.D.
Chief of Hematology
Professor of Pediatrics
Hospital for Sick Children
Toronto, Ontario
Canada

Editor's Note: Donations can be sent directly to Dr. Freedman's lab for tax deductible receipt or to the Neutropenia Support Association Inc. (for tax deductible receipt). Mark your cheque Neutrophil Research, please.

The Canadian Unrelated Bone Marrow Donor Registry: A Program At the Crossroads

Submitted by:
Cam Hobson M.D.
Chair, National Advisory Committee, UBMDR

INTRODUCTION

The Canadian Red Cross Unrelated Bone Marrow Donor Registry (UBMDR) program will celebrate its Tenth Anniversary in 1998. For much of its nearly ten years of existence, the most poignant descriptions of it read: "the little program that could" or "the jewel in the crown of blood". The former insight is testimony to the volunteers and staff who have laboured to bring the very best out of the sometimes distressing environment in which they found themselves. They know that whatever is at the core of this program, it has grasped their hearts and will not let go. Travelling repeatedly across the country to meet with staff or volunteers, one is struck by the deep sense of commitment that motivates them to go that extra step despite the personal cost.

The latter expression touches on the very human engines that drive this program forward, no matter what the odds. They are Hope and Love. There is a motto in the program that says: "Hope sees the invisible, fools the intangible and achieves the impossible". As much as one may describe the program in terms of its medical, statistical and scientific parameters, its customers view the program as a means of expressing hope. The physicians who make requests for a match for their patients do so in hope for a match for their patients do so as a final attempt to secure life. On a daily basis, family and friends of patients come to the program in the hope that the lives of their loved ones may be saved.

On the other end of the "customer" spectrum, there are the bone marrow donors who commit to providing their marrow despite the risks associated with a general anesthetic, or in some cases, the yet unknown factors involved in administering the human growth hormone GCSF. - All of this is done willingly because the donor knows that somewhere in the world there is a patient whose life depends on their commitment to share this vital part of themselves, Bruce Denniston's donor describes being chosen as "Equivalent to having your lottery ticket listed as a winner'. Conversely, one of the inextricable phenomenon in the program is "donor grief, which occurs when a transplant patient dies. The donor often feels a profound sense of loss, which is not infrequently transmitted as well to the staff. It would appear that in this commonplace world, the rarity of matching one human's molecular structure to that of another human's DNA is cause for a profound revelation of what binds us together as a human family yet which distinguishes us as unique individuals.

PROGRAM HISTORY

On one of those shining occasions when medical science combines with community spirit, the necessary forces came together to create a National Unrelated Bone Marrow Donor Registry for the country. In 1987, Bruce Denniston, a young RCMP officer, stationed in Powell River, B.C. developed leukemia, and required a bone marrow transplant to have a chance to survive. His fellow officers and friends in the community, determined to do whatever was necessary to start a bone marrow registry, set about to enroll donors, and raise the necessary funds for its support.

At the same time, Dr. Hans Messner, the "father" of marrow transplantation in Canada, was pursuing the goal of establishing a National Unrelated Bone Marrow Donor Registry. With his colleagues, an approach had been made to the Federal/Provincial Advisory Committee on Institutional and Medical Services for the necessary regulatory approval,

Meanwhile, Dr. Noel Buskard, Medical Director at the Red Cross Blood Transfusion Service in Vancouver, was persuaded to prepare a detailed proposal for establishment of a bone marrow registry under the Canadian Red Cross Society, which was submitted in 1988 to the Canadian Blood Committee (CBC), and reviewed, in consultation with the Federal/Provincial Advisory Committee on Institutional and Medical Services.

The community campaign had become province-wide, with RCMP and municipal police participating enthusiastically, raising over $150,000 for the Bruce Denniston Bone Marrow Society. With a commitment from the B.C. Government for dollar-for-dollar matching funds, and a generous donation from the Woodward Foundation, $600,000 was provided by British Columbians to launch the registry through purchase of special equipment, supplies and provision of technicians' and coordinators' salaries.

In early 1989, although he had received his marrow transplant, Bruce Denniston passed away from associated complications. Despite this, the members of the Bruce Denniston Society, supported by many members of the force, vowed to persevere in their endeavors to develop the registry. (Raising almost $1.4 million to date) That year, the CBC approved the budget for the establishment and operation. A 3-year funding agreement by provincial and territorial governments was announced with a commitment of $2.25 million, based on per capita contributions. A target of 100,000 donors to be recruited over 3 years was reduced to 50,000 by the Conference of Deputy Ministers of Health upon recommendation by the CBC, with the proviso

that "this number may be increased at a later date". The Deputies also endorsed the location of the Canadian national search coordinating centre (CNCC) in Vancouver, and the designation of Red Cross Blood centres with apheresis programs as appropriate bone marrow donor recruitment centres. By May 1990, 10 recruitment coordinators were appointed in Vancouver, Edmonton, Calgary, Saskatoon, Winnipeg, London, Hamilton, Toronto, Ottawa, and Saint John, with later expansion to Montreal and Quebec City. Office space was often makeshift, staff inexperienced, and funding inadequate, but the dedicated commitment of staff and volunteers continues to support remarkable expansion of this unique program.

THE PROGRAM NOW INTO THE 21st CENTURY

Today, with more than 160,000 donors, the Registry responded over the past year to approximately 225 Canadians patients in need of bone marrow transplant, and more than 500 international patients seeking a donor match. This demand on the program comes from a need far exceeding the vision of the founders of the registry. Treatment is now possible for not only the resistant leukemias, but a host of other diseases - other cancers, and multiple hereditary or acquired bone marrow conditions.

Despite successfully coping with the unanticipated load, the program is not without its significant difficulties. Having been embedded in the National Blood Program ($300 + million budget), the UBMDR program (less than $3 million) struggles to maintain its identity and to maintain and advocate the special interest of its customers, patients and donors.

Problems that have plagued the program include:

- failure to recognize Blood Services and UBMDR as distinctly different businesses.
- UBMDR program staff reported to blood managers, who were often more concerned with blood program issues. This caused lack of cohesive teamwork, and lack of management focus to address customer concerns.
- Inability of bone marrow program to respond to a dynamic marketplace.
- Lack of uniform national standards in policy and operating procedures.
- Cross subsidization between the blood program and UBMDR program.
- Low staff morals and high turnover due to inconsistent inappropriate job classification.
- inadequate reinvestment in information systems, leading to threatening overload of computers.
- inability, due to lack of funding, to provide training and quality assurance.lack of consumer involvement.

However, not all is bleak. Due to the exceptional efforts of staff in the program, the UBMDR Advisory Committee was reconstituted in August 1996. Composed of significant stakeholders - transplant physicians, relatives of transplant patients, an ethicist, a donor, a DNA specialist, a business woman, and others representing both donor and patient advocates - the committee has set out to define and recreate a vision of the ideal program to respond to the customers' needs.

"Hope sees the invisible, fools the intangible and achieves the impossible"

The first act of the Advisory Committee was to recognize the need to shoot for the stars. Management Staff were charged with the responsibility to compose a business plan that would position the Registry to become among the best in the world. In-depth consultation with key personnel in the field revealed that there were five quality components essential to such a program:

1. Donor commitment.
2. Speed of the registry.
3. Equality of access to the registry by both donors and patients.
4. High resolution typing - quality laboratory standards.
5. Product safety.

For the first time in its history, the essential nature of the program was defined. Unlike the blood program, which is essentially biological pharmaceutical / manufacturing-based, the UBMDR program is best described as a clinical - based, special DNA registry, sharing no common elements with blood. Thus, without the proper allowances for it to behave as a clinical-based business, unnecessary risk will accrue. For example, the regulatory environment currently being introduced in Blood Services threatens to be at odds with the guidelines/regulations being proposed for transplantation. Besides the requirement for a distinctive stream of quality assurance, there is the fact that the customers of the UBMDR are not defined by geography. Donor to patient delivery of service is not provincially nor regionally bounded, and is not only national, but international, as well. Management according to provincial or regional protocols, rather than national and international standards would detract from demanding logistical requirements and potentially jeopardize patient outcome.

A major defining characteristic of the program is that it is primarily volunteer driven. To make the program evenly accessible to its customers (ie: patients) the program must be able to reach out to Canadians no matter where they live. Just recently the Bruce Denniston Bone Marrow Society sponsored a recruitment campaign in Glace Bay, Cape Breton Island. This is an excellent example of one community, Powell River, B.C., reaching out to another community, Glace Bay, N.S. to build awareness and recruit donors for the National registry. The fact that both towns are coastal communities, and in their reach span the vastness of this country, is testimony to the program being supported by a caring community on a National scale. Far from the registry being just a list of names on a data base, the UBMDR is a series of communities who have mobilized themselves to sponsor members of their societies into the registry. Attrition due to loss of interest is the greatest threat to a quality registry. Only by defining the registry in the context of community will ongoing support be ensured to keep donors interested and committed to their original inspiration of reaching out to help others.

So, in the wake of the blood debacle, if one were to ask the question, "In what new home should the UBMDR program reside?", the answer is clear: certainly, it must be removed from the shadow of

blood. It must avoid becoming a government agency prone to bureaucracy. Rather, as a clinical and volunteer program it must remain close to its customers and responsive to their needs from coast to coast, as well as the needs of its international patients and donors.

The program must be able to encourage the development of affiliated technological advances by supporting research into Stem Cell and Cord Blood applications, which would supplement marrow transplant applications.

It is vital to recognize and enhance the natural linkages to other national organizations such as The Candlelighters Childhood Cancer Foundation, The Leukemia Research Fund, The National Cancer Society, The Neutropenia Support Association Inc., the Canadian Blood and Marrow Transplant Group (of Transplant Physicians), and the many more stakeholders who have an interest in the development and maintenance of a first quality bone marrow transplant program. Only strong representation by these groups before Provincial and Federal Governments will ensure that Canada will have the best possible bone marrow registry program to serve the needs of Canadian patients and their donors, and those of our international customers.

Future possibilities of application of marrow and stem cell transplant technology are expanding exponentially. Research is proceeding at a whirlwind pace, with mind-boggling potential for treatment of immune system diseases and additional hereditary and malignant conditions. A strong, well-managed Registry, administered by a qualified, focused board under appropriate National standards is essential for Canadians to receive the full benefits possible from this unique technology.

Cam Hobson M.D.
Chair, National Advisory Committee, UBMDR

Important Information from our Ontario Chapter

Bone Marrow Procedure

Shirley Cox

Adult

A very painfully invasive procedure which is absolutely necessary.

For Neutropenia patients receiving Neupogen treatment, according to the protocol of the drug, a bone marrow procedure must be performed each 12 months. This test is absolutely necessary in order to detect any changes in your blood, either good or bad.

The procedure for an adult is far more involved than for a child as an adult's bones are mature and firm, whereas a child's bones are in the younger years still in the growth and development stages and are relatively soft. Regardless of age the most important factor is to find the doctor, whom by recommendation has the "best and most experienced hands". The Bone Marrow procedure stress and pain can be kept to a minimum with the skill of the doctor with the best track record in your hospital. Do not be afraid to ask the nurses whom they recommend.

Adult - The procedure is usually done in the area of the middle lower back near the hips. The area is frozen to eliminate the pain of the procedure in the skin area. There is no way to freeze the bone itself. A small finger drill is used on the bone to actually drill a hole into the bone so that the marrow can be removed. The whole procedure should be in the neighborhood of a minute or so with additional time spend in prep time for freezing etc. Once the drilling and marrow is removed, the pressure is removed and so is the intense part of the pain. The area will remain tender but not a source of pain.

Child - Since the bones are still developing they are soft enough to pierce with a procedure needle and depending on the age of the child the procedure may be conducted in several different ways.

Infant - Instead of the trauma of two needles, the first being the freezing of the surface skin and the waiting for the effect to take place, you may elect to forgo all freezing and just do the procedure, keeping in mind that the pain is only whilst the pressure is put on the bone itself. This procedure will take less time and in the hands of an experienced doctor like mine, I would guesstimate that he has performed it in under 10 seconds. My child was fine once out of the procedure room and never complained.

Toddler - (old enough to remember the last bone marrow procedure) Freezing of the skin and or a mind sedation may be recommended so that they have no recall. This is a conscious sedation — child will be wobbly but awake; lights on but nobody home sort of thing.

Older child - If the child is old enough and knows what is coming, and the conscious sedation route is meeting with stress, tension, apprehension then you may wish to make arrangements for the child or teen to be sedated.

Keeping things in perspective

It would take you longer to recite your full name, address and telephone number than it would to have a bone marrow procedure.

Remember what your life was like before Neupogen — I guarantee that a few seconds of pain far outweighs the fevers, infections, pain, and constant fighting for your life that you use to endure. How soon we forget.

Testing for Osteoporosis

Some persons have been found to be dealing with a depletion of their bone density whilst taking Neupogen. This is a common condition called osteoporosis, a weakening of the bones. With proper exercise, diet and rest you can win the fight against osteoporosis if you are diagnosed in the early stages.

The testing is very specialized and a hospital, usually a women's hospital, is the only likely source of a bone density scanning bed. In Toronto Ontario the closest hospital to Sick Childrens that have this xray machine is at The Toronto General. The testing is non-invasive, you are gowned and lay on a flat bed like table for 5 minutes whilst a large arm xray "jumps" back and forth overtop of you. This is a full body xray and the only requirement is that you remain still.

Shirley Cox
Chairperson Ontario Chapter
Neutropenia Support Assoc. Inc.
1-705-424-1285

Excerpts from a few research papers


Dr. David Dale

Non-malignant Neutropenia

E. L. Sievers, D. C. Dale

Introduction

To meet normal physiologic needs, a healthy adult produces roughly 60 billion neutrophils each day. While neutrophils are produced by the bone marrow at a prodigious rate, their blood half-life is short - on the order of approximately 8 hours in a normal individual. Hence, erythrocytes, with a far longer lifespan, vastly outnumber neutrophils by a ratio of about one thousand to one in the peripheral blood. Under normal physiologic conditions, a stable equilibrium exists between marrow neutrophil production and peripheral utilization. When the production of neutrophils by the bone marrow is outpaced by utilization in the periphery, the number of circulating neutrophils in the peripheral blood decreases and Neutropenia results.

Normal neutrophil levels vary with age and race. In general, these counts range from 1.8 to 7.0 x 109/L, with a mean of approximately 4.0 x 109/L. Infants between 2 weeks and 1 year of age have neutrophil counts that are normally somewhat lower than older individuals. Additionally, people of African origin have normal neutrophil counts that are slightly lower than those seen in Caucasians. When a patient is found to be neutropenic, the peripheral blood neutrophil count serves as a rough guide to the relative seriousness of the disorder. This degree of Neutropenia can be "mild"(1.0 - 1.8 x 109/L), 'moderate'(0.5 - 1.0 x 109/L), or 'severe' (less than 0.5 x 109/L). It should be emphasized, however, that the duration of Neutropenia, the function of neutrophils and other host defenses, and the capacity of the bone marrow to respond also contribute considerably to the relative susceptibility of a patient to infection.

Patients with severe Neutropenia, and particularly those with neutrophil levels less than 0.2 x 109/L, are at significantly increased risk of infection due to invasion of surface bacteria in the mouth, intestinal tract or skin. Such patients frequently demonstrate mucosal inflammation, particularly of the gingival and perirectal areas and often manifest cellulitis, abscesses. furunculosis, pneumonia or septicemia. Unlike normal individuals, infections in these individuals often lack the fluctuance, induration, and exudate that typically accompany a normal inflammatory response. While superficial infections cause substantial morbidity in these patients, deep-tissue infections of the sinuses, lungs. Liver and blood pose the greatest risks. Resistant organisms caused by the repeated use of broad spectrum antibiotics often complicate treatment.

ACUTE NON-MALIGNANT NEUTROPENIA

Infection

Table 1 Causes of non-malignant Neutropenia

Infection	Human immunodeficiency virus
Immunologic diseases	Parvovirus
	Hepatitis viruses
	Malaria
	Isoimmune neonatal Neutropenia
	Autoimmune Neutropenia
	Felty's syndrome
	Rheumatoid arthritis
	Sjogren's syndrome
	Systemic lupus erythematosus
Drug-induced Neutropenia	
Hematologic diseases	Congenital Neutropenia or Kostmann's syndrome
	Cyclic Neutropenia
	Childhood idiopathic Neutropenia
	Adult idiopathic Neutropenia
	Shwachman's syndrome
	Myelokathexis syndrome
	Congenital immunologic deficiency syndromes
	Aplastic anemia
	Myelodysplastic syndromes

Acquired non-malignant Neutropenia occurs much more commonly than chronic Neutropenia. In children, the acute forms are most frequently seen in association with viral infection. Neutropenia in this setting usually develops over one to two days and can persist for up to a week without serious sequelae. Since concomitant diminution of other cell lines in this setting is unusual, evaluation for malignancy should be considered if the red cell or platelet compartment are also significantly decreased. In the seriously ill patient - particularly the neonate - sepsis can cause acute Neutropenia. Since such patients can deplete their neutrophil reserves during an overwhelming infection, granulocyte transfusions may be life-saving.

Isoimmune neonatal Neutropenia

Analogous to Rh hemolytic disease of the newborn, isoimmune neonatal Neutropenia results following maternal sensitization to fetal neutrophil antiogens during estation. Antibodies freely cross the placenta, destroy infant neutrophils, and predispose these affected children to serious infection. Commonly cutaneous infections are seen but, occasionally, respiratory tract or urinary tract infections occur. Bone marrow evaluation usually shows a relative myeloid hyperplasia, with an unusually decreased number of mature neutrophils. Often, a specific maternal neutrophil antibody is identified that reacts with the father's neutrophils. Most com-

monly, antibody is directed against paternal NA1 or NA2 which is inherited by the fetus. Since the half-life of circulating maternal IgG is approximately 7 weeks, the child's Neutropenia usually resolves by about 2 months of age. Antibiotics serve as the foundation of treatment of this disorder. In seriously ill neonates, transfusion of maternal granulocytes might be considered.

Autoimmune Neutropenia

Severe acute Neutropenia discovered in older children and adults unassociated with an acute viral syndrome may represent autoimmune Neutropenia. However, demonstration of neutrophil antibodies is required to differentiate this disorder from benign chronic idiopathic Neutropenia (see below). Physical examination in these patients is usually unremarkable, but occasionally splenomegaly is noted. Marrow findings generally reflect that of 'bone marrow arrest' - where adequate numbers of early myeloid cells can be identified, but more mature myeloid elements appear lacking. The level of this 'arrest' seems to vary between patients, and may reflect patient variability with regard to the myeloid antigen (early versus late) targeted by autoantibodies. Since young patients with autoimmune Neutropenia are likely to have a relatively benign course, most do not appear to require treatment of any kind. In patients with recurrent infections, treatment with corticosteroids results in improved neutrophil counts in about half of patients. The majority of patients less than 2 years of age spontaneously achieve a durable remission within 3 years of their initial diagnosis. In contrast, adults and children over the age of 2 tend to have accompanying immunologic abnormalities and appear less likely to improve spontaneously over time. Similarly, older patients appear more resistant to therapeutic interventions including corticosteroids, intravenous immune globulin, and splenectomy. Two patients have achieved clinical improvement with cyclosporine.

Drug-induced Neutropenia

This grave and unpredictable disorder is characterized by severe Neutropenia caused by an idiosyncratic reaction to a drug that results in either direct suppression or immune destruction of neutrophils or myeloid precursors. Historically, women and older individuals experience these reactions more commonly than men and younger patients. In addition, genetic factors appear to influence a particular individual's tendency to develop this type of reaction. Typically, Neutropenia becomes evident 1-2 weeks following an initial exposure to a drug, or swiftly following a recent re-exposure to an offending agent. Treatment consists of rapid withdrawal of any drug suspected of causing the idiosyncratic reaction. Unfortunately, therapy with corticosteroids has not shown significant efficacy. A partial list of drugs that have been associated with drug-induced Neutropenia is provided in Table 2.

Table 2 Drug-induced Neutropenia: a partial list of offending agents

Antibiotics
Chloramphenicol
Penicillin
Sulfonamides
Antithyroid agents
Propythiouracil
Tranquilizers
Chlorpromazine
Phenothiazines
Analgesics/antiinflammatory agents
Aspirin
Acetaminophen
Phenylbutazone
Antirheumatics
Gold
Levamisole
Penicillamine
Sedatives
Barbiturates
Benzodiazepines

SEVERE CHRONIC NEUTROPENIA

Severe chronic Neutropenia (SCN) is a global, descriptive term for several disorders in which neutrophil levels are consistently or recurrently at levels less than 0.5 x 1O9/L. As congestive heart failure has varied etiologies, SCN describes a group of diseases with multiple causes. Despite this heterogeneity of origin, administration of exogenous myeloid growth factors to individuals with SCN results in an increase in neutrophil counts in most patients. Hence, treatment of this group of disorders will be considered as a separate topic at the end of this section.

Congenital Neutropenia

Congenital Neutropenia, or Kostmann's syndrome, is a form of SCN. Kostmann, a Swedish physician who described a large family with several severely affected members, originally described this disease entity in 1956. Inherited in both an autosomal dominant and recessive manner, this syndrome is most often recognized at birth or shortly thereafter because of significant fever and infection. Oomphalitis, cellulitis, and perirectal abscesses are particularly common. Morphologic examination of bone marrow from these patients usually reveals almost no evidence of developing neutrophils beyond the promyelocyte stage. However, formation of monocytes and eosinophils usually remains normal. In vitro cultures demonstrate adequate numbers of colony forming cells (CFCGM), in which normal maturation of progenitor cells into mature neutrophils variably occurs. Upon the exposure to supraphysiologic levels of recombinant human granulocyte colony stimulating factor (rHuGCSF), however, these CFC-GM often form mature neutrophils. While this observation might suggest impaired synthesis of G-CSF in these patients, biologically active levels of this cytokine are usually elevated or normal. Hence, the G-CSF receptor somehow fails to transduce its signal appropriately.

G-CSF receptors appear normal in number and binding affin-

ity in almost all patients evaluated. However, occasional children with Kostmann's syndrome - almost all in transition to AML - have been shown to manifest abnormalities of the receptor for G-CSF. In these rare cases, somatic mutation in one of the two alleles prevents function of the receptor encoded by the remaining normal allele. This mutated receptor appears to disrupt the normal regulation of myeloid growth, and might facilitate the evolution of leukemic subpopulations. It should be emphasized, however, that for the large majority of patients with Kostmann's syndrome, no obvious defect has been detected — suggesting a postreceptor problem.

Cyclic Neutropenia

This rare congenital disorder is characterized by remarkably regular oscillations of the blood neutrophil count. Usually with a periodicity of approximately 21 days. Frequently, cells of all hematopoietic lineages cycle as well. Periods of Neutropenia usually last for 3-6 days. During this time, there are usually no identifiable mature neutrophils present in the peripheral blood. Patients usually anticipate these periods of Neutropenia because they notice increasing anorexia and malaise. They often complain of headaches and myalgia when the neutrophil counts nadir and pharyngitis and oral ulcerations are common physical findings. While some patients occasionally develop severe, life-threatening infections, most adapt well to these periods of illness and experience relatively few chronic problems. Usually, when the neutrophil counts return to levels greater than 0.5 x 109/L, patients report an improved sense of wellbeing, an increased appetite and the appearance of a yellowwhite exudate over the ulcers of the mouth and tongue.

While a third of patients appear to inherit the disorder in an autosomal dominant pattern, the majority of cases seem to occur sporadically. Most patients experience the onset of symptoms in infancy or childhood, but in 3 individuals, the initial diagnosis notably occurred late in life. Two features are necessary to confidently make a diagnosis of cyclic Neutropenia: (1) regular, cyclic fluctuations in peripheral blood neutrophil counts with a period ranging from 19 to 21 days and (2) documentation of neutrophil counts of less than 0.2 x 109/L during periods of Neutropenia. In instances where the fluctuations do not appear regular, and severe Neutropenia is absent, it is best to regard the diagnosis as idiopathic or obtain additional clinical and laboratory data. At a minimum, 3 complete blood counts with differentials should be observed weekly for 6-8 weeks to discern the characteristic cycling and severe Neutropenia seen with this disorder.

Chronic idiopathic Neutropenia

This heterogeneous diagnostic category is one of exclusion. It includes patients with a normal past history, generally including a previously normal complete blood count. These patients cannot carry the diagnosis or have received treatment for a malignant or premalignant hematologic disease, or a recognized infectious or immunologic disease. Often, the Neutropenia is identified on routine blood counts without accompanying symptoms or signs suggestive of infection. However, skin, perirectal, and oral infections can be reported in the history as well. Normal numbers of platelets and red blood cells are present, but these patients often demonstrate a moderate increase in their monocyte count. While morphologic examination of the marrow aspirate demonstrates variable findings, this procedure is recommended for the purpose of evaluating for malignancy. The diagnosis of chronic idiopathic Neutropenia in children merits special mention. This disorder tends to follow a remarkably benign course and often resolves spontaneously. However, it is particularly important to exclude autoimmune diseases and myelodysplastic syndromes in these patients. While demonstration of neutrophil antibody suggests an immunologic mechanism for Neutropenia, these tests have not been shown to predict clinical outcome, nor whether a patient will respond to cytokine therapy. Since this entity usually follows a benign course, it is not clear whether cytokine therapy should be routinely instituted in these patients. On balance, children experiencing multiple infections during periods of Neutropenia would appear to benefit from chronic administration of rHuG-CSF Conversely, rHuG-CSF therapy might be avoided in healthy children with chronic Neutropenia until insights regarding the potential risks of prolonged therapy are gleaned.

Shwachman's syndrome

Severe Neutropenia also occurs in Shwachman's syndrome (Neutropenia associated with exocrine pancreatic insufficiency, metaphyseal chondrodysplasia, and dwarfism). This rare disorder is inherited in an autosomal recessive fashion and usually presents in the neonatal period. Neutrophil counts vary from 200 to 400 per ul. A paucity of maturing neutrophils is usually noted on morphologic evaluation of the marrow aspirate." Often confused with cystic fibrosis, these patients do not typically demonstrate abnormal pulmonary findings. Some patients with Shwachman syndrome have developed severe aplastic anemia and rarely, leukemia.

Myelokathexis syndrome

Myelokathexis syndrome is an extremely rare disease characterized by chronic moderate Neutropenia and an increased incidence of infections. The diagnosis of this disorder is based upon the identification of hypersegmented nuclei and cytoplasmic vacuoles in mature neutrophils and marked hyperplastic changes seen in the bone marrow. Characteristically, the marrow demonstrates degenerating granulocytes suggesting an increased intramedullary obliteration of neutrophils as one possible mechanism for Neutropenia.

Congenital immunologic deficiency syndromes

Various rare congenital immunologic deficiency syndromes are associated with Neutropenia. Usually, these patients have a coexisting T-cell deficiency as well. Reticular dysgenesis is an extremely uncommon hematopoietic stem-cell disorder that results in an absence of cells of lymphoid and myeloid lineage. If instituted early, bone marrow transplant has successfully corrected this disorder.

AUTOIMMUNE LEUKOPENIA

Gordon Starkebaum, M.D.
David C. Dale, M.D.

The terms "autoimmune leukopenia," "autoimmune granulocytopenia," and "autoimmune Neutropenia" arc often used synonymously to describe conditions in which autoantibodies to mature neutrophils, or their precursors, lead to cell destruction and a reduced blood neutrophil count. Leukopenia is generally defined as a reduction in the total white blood cell count to less than 4,000 cells per deciliter; Neutropenia is defined as a neutrophil count of less than 1,800 cells per deciliter. Neutropenia has numerous causes and mechanisms; the most frequent cause is reduced cell production by the bone marrow. Neutropenia also occurs because of abnormalities in the distribution of cells between the circulating and marginated pools of cells in the blood and accelerated cell destruction. Autoimmune leukopenia can be caused by any of these mechanisms.

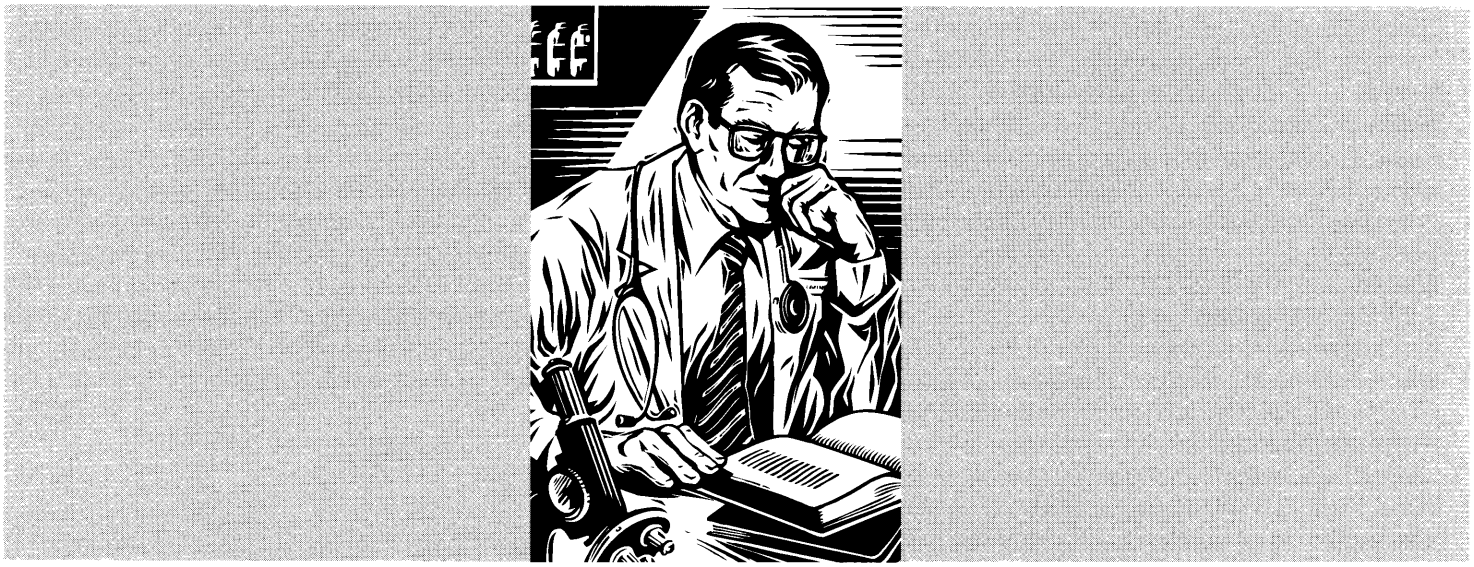
Although the term "leukopenia" often implies "Neutropenia," there are many pathologic conditions in which not only neutrophils but also lymphocytes, monocytes, eosinophils, and basophils are concomitantly or specifically reduced. Lymphocytopenia is a common feature of the stress response to many infections and acute inflammatory illnesses. It occurs in systemic lupus erythematosus (SLE) and other collagen vascular diseases. Lymphocytopenia, monocytopenia, and eosinopenia are regularly seen with corticosteroid therapy. Reductions in any of the white blood cell elements may reflect an important ongoing pathologic process. Severe Neutropenia, that is, fewer than 500 blood neutrophils even room temperature cells in small peripheral vessels during the transfusion can result in severe ischemic changes and vascular compromise.

PATIENT EVALUATION

Evaluation begins with a careful history and physical examination. The family history is important; it may reveal other individuals with recurrent fevers, infections, and leukopenia, as well as previously diagnosed autoimmune diseases. The drug history and current medications are also extremely important. The physical examination should give special attention to the skin and mucous membranes, especially the gingiva, oropharynx, and perianal areas. Examination for arthritis, lymphadenopathy, splenomegaly, hepatomegaly, and bone tenderness are also very important.

Laboratory examination begins with a complete blood count. Measurement of the hematocrit and hemoglobin, reticulocytes, and platelets are helpful to recognize serious hematologic diseases such as aplastic anemia, myelodysplasia, or leukemia. A bone marrow aspirate and biopsy may also be necessary. It may also be helpful to obtain serologic tests for autoimmune diseases such as antinuclear antibodies, rheumatoid factor and other specialized tests; liver function tests; and tests for chronic viral infections, including hepatitis, infectious mononucleosis, and HIV. Results from these tests will direct further work-up and consultation, and assays for antineutrophil antibodies generally follow these preliminary assessments.

Measurements of neutrophil kinetics (i.e., glucocorticosteroid test of the bone marrow reserves), epinephrine infusion to measure the degree of neutrophil margination, and radioisotopic studies to measure neutrophil turnover are best performed by research laboratories. Measurement of the growth of bone marrow cells with in vitro culture systems is also a specialized procedure. Many clinical laboratories now examine the immunophenotype of blood leukocytes; this procedure may be useful in identifying clonal disorders of the immune system such as the large, granular lymphocyte syndrome that is associated with Neutropenia.



Words from Our Hardworking President

Lorna Stevens

The Neutropenia Support Association Inc., a registered Canadian charity, was formed in 1989. Our main goal at that time was, and continues to be, education, research and support. As volunteer activists, we have been involved in a continual process to help influence change in a manner that is fair and equitable both provincially and federally involving all political parties.

We have responded to many inquiries pertaining to the safety of our blood system and over the years we have followed with great interest the status of the nation's blood supply. It has been said that the risk of infection via blood products is low, it is never said to be zero. All blood and blood products used in Canada are tested for infectious diseases 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 intravenous gamm-globulin (IVIG) can be successfully used 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). IVIG has been used in the treatment of autoimmune Neutropenia of infancy, but is not a front line therapy for severe chronic Neutropenia. Neutropenia presents in over twenty other diseases and IVIG may have a benefit to patients who have a coexisting immune defect resulting in low immunoglobulin levels.

When the Red Cross notified families of the potential hazard of tainted blood, we started to share numerous articles and answer blood related questions with the help of our medical advisors.

In 1995, Lorna Stevens accepted the opportunity to sit on the Advisory Council to the Federal / Provincial / Territorial Initiative on Blood (travel expenses paid for by Health Canada). Simply put, the purpose of the consumer advisory council has been:

- To serve as a forum for the Canadian public to receive information from and provide input to the blood system.
- To provide advice and recommendations which would help the blood system ensure its needs are in the best interest of all consumers.

Lorna has attended all meetings and conferences the CAC has initiated and has met with the Federal Health Minister, Allan Rock, as well as the Bureau of Biologics and Radiopharmaceuticals (BBR) to discuss issues and concerns that regard blood supply, safety standards and regulations in Canada.

Addressed (1996 - 1997):

- F/P.T. Group as it relates to Krevor
- Blood, Blood Products, Alternative Treatments and Options
- Response to Harm
- Adverse Reactions
- Blood Supply Utilization and Management
- Medical Trends
- Surgical Trends
- Accountability and Transparency
- Regulatory Issues, Monitoring, Inspection, Licensing, Staffing, Funding
- Key Functions of the Blood Collection and distribution system
- Ongoing Consumer Participation and Representation
- Recruitment of Donors to ensure a safe, adequate blood supply
- And many other Blood Service Issues

The multidisciplinary conference (T.O.), November 3rd and 4th, 1997 was the first National step toward building a consensus among key participants on recommendations for a blood system which will meet the needs of Canadians. Participants (181) included medical professionals, health care providers, consumers, government and industry.

The Top 12 Recommendations are:

1. Mandatory and standardized education on transfusions and alternatives at, 1) undergrad, 2) post grad, 3) continuing education for physicians

   Primary Responsibility
   1. Medical Schools
   2. Royal College
   3. Provincial Colleagues

2. Put "safety is paramount" into words and action, including:
   - CBS articles of incorporation, corporate culture, management, involvement of consumers;

     transparent, agreed-upon, timely decision-making process for determining safety (including science, ethics, cost, whole health system needs);
   - up-to-date technology, standards and guidelines for detecting, screening and removing pathogens;

   Primary Responsibility
   CBS
   Professional Bodies
   F/P/T Departments of Health

3. Education of health care professionals, consumers, donors, and general public to be delivered locally based on national standards and guidelines;

4. Alternatives (both substitutes and pharmaceuticals influencing the use of blood) be funded within the same envelope as blood;

   Primary Responsibility
   CBS (P/Ts)

5. Explore the role of no-fault scheme as part of building public confidence;

   Primary Responsibility
   Federal and Provincial Governments

6. To establish an advisory committee to the Board of the CBS which would have the mandate of developing standards. This committee would link with specific diseases and associated user groups for input in developing evidence-based

standards. These groups to include allied health professionals, patients and other stakeholders;

Primary Responsibility
Board of CBS

7. We recommend the development of an effective utilization management system that emphasizes local (hospital/ users) monitoring of blood usage based on nationally derived guidelines. The system requires clarification of the roles and responsibilities and provide positive incentives for participants in supply, utilization and inventory management;

Primary Responsibility
Federal
Government
Hospitals
Medical Personnel
Consumer / Patients

8. To develop an integrated data management system on a national basis that would be linked to hospitals. Such a data system could include information about blood donation, manufactured products, indication for transfusion, adverse events and patient outcomes;

Primary Responsibility
Board, with linkages to hospitals.

9. We recommend the development of a transparent costing system for blood product consumption. Such a costing model can be used on a local level for utilization monitoring and information dissemination to users/policy makers.

Primary Responsibility
CBS
Provincial Government
Hospitals
Medical Personnel
Consumer/Patients
Industry

10. Implement an information system to provide: surveillance (known and emerging threats); data on adverse events; vein-to-vein tracking; data for local, regional and national needs; information on international trends; usage utilization data;

Primary Responsibility
CBS
Local, Provincial, Federal Departments of Health

11. As part of hospital accreditation and regulation, a system must be in place to capture and make available data on transfusion utilization and outcomes;

Primary Responsibility
Hospital Transfusion Service

12. "Vein-to-vein' record keeping with computer links between hemophilia centres, blood banks and CBS for forward and backward tracking;

Primary Responsibility
CBS - later Food & Drug Regulations

Recently, Lorna Stevens has been invited to sit on an Expert Working Group on Safety of Blood and Blood Components for Transfusion. The Therapeutic Products Directorate is undertaking to facilitate the development of national, safety standards based on a risk assessment / management approach, within a standards-based regulatory framework. Costs of her voluntary participation will be met by the T.P.D. The inaugural meeting is scheduled for December/97.

The Consumer Advisory Council's first three principals are:

- The Consumer Advisory Council's first priority is to serve in the best interest of all Canadians.
- The Consumer Advisory Council is accountable to the Canadian Public, firstly, and to the consumer organizations which it represents, secondly.
- The Consumer Advisory Council will treat each other as equals and operate with openness, fairness and integrity.

With this in mind, Lorna encourages **your** input.

Lorna Stevens
24-hr pager: 1-204-989-5000
or
1-204-489-8454

Excerpt from a letter from Health Canada

...

I am writing to express my sincere appreciation for agreeing to serve as an expert member of the Expert Working Group (or EWG) tasked to develop safety standards for blood/blood components. The EWG-Blood is really a landmark committee and certainly, the objective of drafting and finalizing a "Canadian National Standard for Blood" will be an onerous one. No doubt, it is a task which will have its place in history and one which carries with it a great deal of national responsibility as well as visibility.

...

Support Group expanding the Globe

We have heard of support group development in other countries, primarily facilitated by SCN physicians.

Speaking of the Globe, the Neutropenia support Assoc. Inc. Web-Site has been a tremendous success. Just recently we hit the 1000 mark on the number of inquiries to this site. Our goal is to have all of our newsletters online for the world to see. If possible we would like to have all of our information there. If you have something you would like to see, or comment on, please let us know. E-mail us at carlsonm@neutropenia.ca or stevensl@neutropenia.ca so don't be shy; check it out, at www.neutropenia.ca

Provincial government returns our call

The following is excerpts from a letter received from the Minister of Health in response to our 1996 newsletter MCTRF advocacy campaign.

This is in response to your letter to Premier Filmon and myself concerning the suspension of the Manitoba Health Capital Construction Program and the Pharmacare Drug Program.

First, I would like to acknowledge and commend you on the commitment and caring that you have demonstrated by being a volunteer. My department and I recognize that the incidence of cancer is increasing and that continued research in cancer prevention and treatment is essential.

A creative solution to the shortcomings of the Olivia Street facility has been found through the cooperative efforts of the Cancer Foundation and my department. The funding commitment to a redevelopment of the facilities at the Manitoba Cancer Treatment and Research Foundation is a recognition of the need to improve and expand the facility for the care of patients from around the Province and to allow the foundation to continue its work in treatment and research.

The Pharmacare Drug Program changes were a response to the need of rationalizing drug program administration and providing financial assistance to those who need it most. In this regard, private insurers will continue to have a role to play.

A Manitoba Drug Use Management Centre is under consideration for many of the same reasons addressed in your letter - escalating drug costs, inappropriate drug use, non-compliance and a need for drug use evaluation. The Centre would be national in scope, with a mandate to promote the optimal cost effective use of medications.

The need for the safety, comfort and dignity of all Manitobans is a shared goal and one we can achieve by working together.

Yours sincerely,
James C. McCrae

A huge Thank you to another Vital contributor to our organization

We wish to wholeheartedly applaud Dr. Cham.

Dr. Cham has been a vital link for our organization almost since our beginning. She has not only been a medical advisor, but has always made herself available to meet any special requests that we might have. This includes national speaking engagements for the International Candlelighters conferences (pediatric cancer support charity), Canadian Cancer Society, our local group meetings and major fundraisers.

Her formal presentations entitled Chemotherapy Induced Neutropenia and "Neutropenia; Causes, Consequences and Care" which are available on videotape are freely available to families worldwide.

She also reviewed the booklets on these same topics and have now been published in both French and English. We receive weekly requests from hospitals and patients for this information.

Dr. Cham helped initiate the Canadian Severe Chronic Neutropenia Registry and in 1993 a group of interested physicians were brought together to establish the SCN International Registry. This physician network assists in the treatment, management, and understanding of this disorder and has helped to establish a database for future research. She is still one of two noteworthy Canadian physicians facilitating the development of this registry.

She is a tremendous asset to our group. Her assistance has been tireless, providing information for our newsletters, answering questions for our " Ask The Doctor" column, as well as for our toll free information line and our Website on the Internet.

Since the Neutropenia Support Association consists of 100% volunteers, we would be unable to provide the valuable and timely help without her professional interest and guidance.

On a more personal level, Dr. Cham brings a level of communication which offers reassurance to children and their families. Many parents have commented on her caring and sincere manner during stressful times. Choices can be extremely difficult and Dr. Cham takes great care in discussing all options available. Rather than feeling helpless, families feel they are part of the health care team.

Thank you, Bonnie!

A Note from the Candlelighters Childhood Cancer Foundation Canada

On behalf of Candlelighters Childhood Cancer Foundation Canada and the Conference Planning Committee for "Childhood Cancer and the Family: Forward to the Future", I would like to thank you most sincerely for your participation at our recent conference. The conference was a great success and there is no doubt that your presentation contributed to the success.

Editors Note: Thanks to Dr. Richard Woodman, Dr. Bonnie Cham, Dr. Melvin Freedman, and Lorna Stevens

A Big Hardy Well Done Gang Fundraiser Update

We have had a number of Fundraisers since our last newsletter.

The **Third Annual Poor Man's Charity Golf Tournament** was held September 26, 1996 at the Transcona Golf Club. This was another smashing success; approximately $7,000 was raised for the Neutropenia Support Assoc. However the weather was not that great, as it rained for most of the afternoon. Despite the rain that day a good time was had by all, a superb dinner, an abundance of prizes and great Karaoke entertainment. Can it get any better than this?? Well it did....

The **Fourth Annual Poor Man's Charity Golf Tournament** held August 21, 1997, again at the Transcona Golf Club out did last year; approximately $8,500 was raised. WOW!! There was a great turnout, over 130 golfers on a beautiful, bright sunny day. Another scrumptious dinner, Karaoke, and tons of great prizes for everyone.

A huge Hardy Well Done Gang for Jim Benzelock, Campbell McIntyre, and everyone that helped make these golf tournaments extremely successful.

Thank You!!

The Neutropenia Support Assoc. would also like to thank the management and staff of the **Transcona Golf Club** for their generous donations, hard work and the use of the facilities for our annual golf tournaments.

Thank you!!

The **Winnipeg Jets Alumni** also held their 8th Annual Heritage Golf Classic, Thursday, June 20, 1996 at the Kingswood golf club, Lasalle, Manitoba. Approximately $1200 was donated from this event. Thank you to all who supported it.

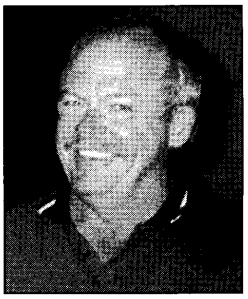
■

Third Annual Poor Man's Charity Golf Tournament, September, 1996 – Trying to stay dry!

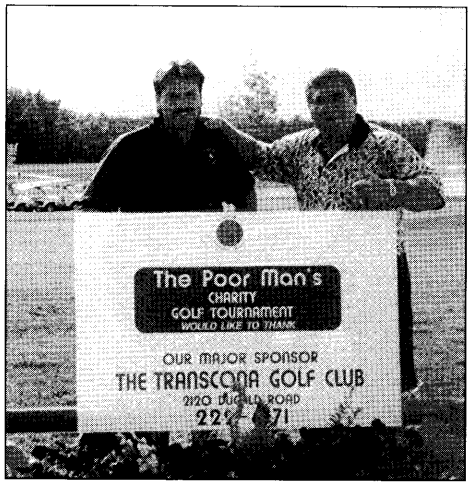
(below) Jamie Benzelock hamming it up with some friends.

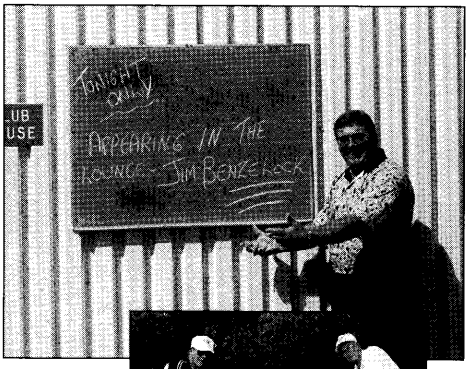
Prizes for all!

Campbell McIntyre



Fourth Annual Poor Man's Charity Golf Tournament August, 1997; Sold out!





United Way of Winnipeg

April 30, 1997.
United Way Donor Directed giving:

Another campaign year has come and gone, and once again we graciously thank donors that have specifically directed their donation to our Registered Charity #0848093-11.

Please continue to pledge us!

May 23, 1997.

On behalf of the donors who contributed through the All Charities Campaign, it is my pleasure to enclose a cheque in the amount of $149.98 payable to your organization. This represents cash and payroll donations made in 1996 by employees of the Province Of Manitoba and its affiliates and pensioners of the Civil Service Superannuation Board who chose to participate.

The Neutropenia Support Assoc. Inc. would like to thank all the donors who named our organization as the beneficiary for their donations.

Should you have any questions concerning the All Charities Campaign, please contact them at (204) 945-5621 Fax at (204) 945-1568 or write to 12th Floor, 405 Broadway, Winnipeg, Manitoba, R3C-3L6

■

Jubilee Chapter #27 Order of the Eastern Star wishes to donate the sum of two hundred and fifty ($250.00) dollars. As one of our charitable donations for 1997 towards the good work of your association.

Editor's Note: The Neutropenia Support Assoc. would like to Thank the Jubilee Chapter #27 for their generous donation of $250 dollars. We look forward to your continued support.

■

"Giving is Rewarding" Thank You to the Winnipeg Club Oldtimers

The Winnipeg Club Oldtimers came through big time again with $4,484.44 raised from their annual Golf Tournament at Rossmere, July 10th, 1997.

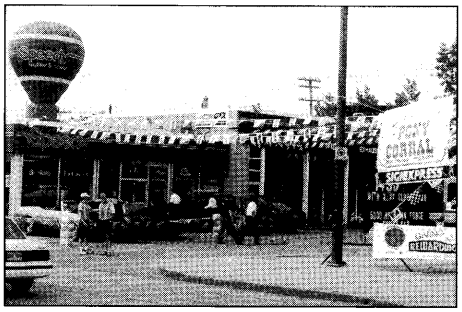
Since its inception, the organization has supported charities like the Children ' s Wish Foundation, the Juvenile Diabetes Foundation, the Christmas Cheer Board, Ronald McDonald House, the Neutropenia Support Association and Dove Homes. What a great way to enjoy a super sport while upholding this tradition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

You are terrific and we Thank You!

Some of the Winnipeg Club Oldtimers

Thanks

to the Pony Corral and Speedy for all your support and the opportunity to participate in this event; approximately $373 was raised.



The Funny Car display

Distributed blood holds risk

Oct 5th/97
Victoria BC Colonist

VANCOUVER (CP) - Approximately 5,000 vials of blood products tainted with a potentially fatal brain disease have been distributed in British Columbia, a Red Cross official says.

"It's hard to estimate, but it's about 5,000 vials," said Dr. Antonio Giulivi, the agency's assistant national director of medical and scientific affairs, who was visiting Vancouver.

However, Giulivi said it's impossible to determine at this time how many people in BC actually got the vials, which contained so-called fractionated blood products - not straight blood.

The tainted blood, which would have been mixed with donations from healthy people, came from a single donor, whose father recently died from an inherited type of Creutzfeldt-Jakob disease - the human form of mad cow disease.

Giulivi said that there is no record of anybody ever contracting the disease through tainted blood.

"This is not a blood scandal. There is only a theoretical risk." As far as we know there's no danger, but we have to notify hospitals because of a policy statement of Health Canada."

The Red Cross has alerted hospitals across Canada that about 200,000 vials were given to about 50,000 people.

The suspect blood products were sent across the country from 1984 to 1993. The donor last gave blood in 1991.

The expiry date on the tainted vials was December 1994 so the contents were either used or discarded by then.

DNA tests have shown the donor, still in good health is a carrier of a gene linked to a hereditary form of Creutzfeldt-Jakob.

Deputy provincial health officer Dr. Shaun Peck said the people who received the blood products could be a wide spectrum.

They include hemophiliacs, people with AIDS or leukemia who needed transfusions, patients in critical care, and travelers to undeveloped countries getting immunity against hepatitis A.

Peck said the ministry is telling hospitals to let recipients know if they received the blood product only if they call and ask.

"We don't think it's necessarily right to notify people, but from a moral point of view, if they want to find out, they should be able to find out.

ACCH CANADA

An Update
January 15, 1997

MEMO TO MEMBERS OF THE CANADIAN ISSUES TASK FORCE

Since our teleconference in September we have had an ACCH Board meeting in Washington, a conference call with members of the Executive Committee, consultations with our legal adviser and we now have a clear picture of how this organization will take shape. It will be made up of two separate but related parts: a national affiliate of ACCH called ACCH Canada, and an independently incorporated organization with a charitable registration number, called the Canadian Alliance for Children's Healthcare - CACH. ACCH Canada will be chartered by ACCH. We have included a set of bylaws for ACCH Canada drafted by Chris Brown, President-elect of ACCH. She based these on the model bylaws for local affiliates. Changes will be needed to address the National and indeed the international character of ACCH Canada within ACCH.

CACH will add the functions that a national affiliate cannot undertake by itself. CACH will raise money in Canada all of which will be used here to address issues in our healthcare delivery systems. The Alliance will reach beyond the traditional membership of ACCH to involve all relevant participants in the healthcare system. Our goal is to foster the best healthcare for Canadian children and families using all available resources. The business of CACH will be to build alliances just as the name suggests.

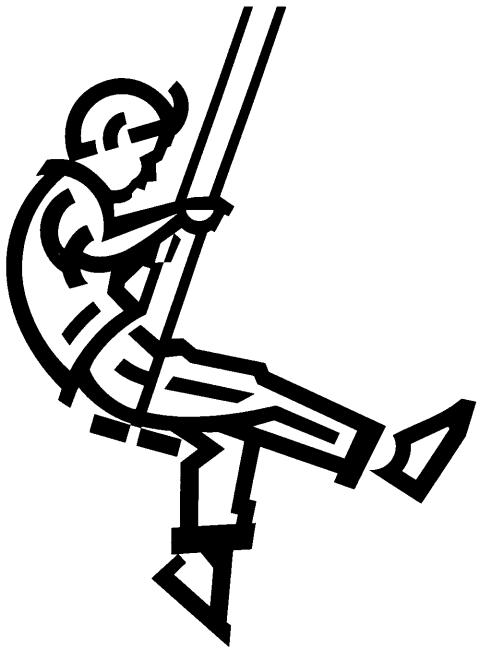
Editors note: for further information please contact

Jean-V. Wittenberg
Dept. of Psychiatry
Hospital for Sick Children
555 University Ave.
Toronto, Ontario
M5G-1X8
416-813-7528 or Fax 416-813-5326
email jwitt@sickkids.on.ca

Breast Feeding is a Good Thing

Our Neutropenia Support Association Inc. is aware of the benefit of reducing infection during breast-feeding.

Many of our children were diagnosed with Neutropenia after breast-feeding ended. Infections were experienced during this period, but the mother's "protection" helped considerably in our opinion.



Parent's Perception of Family-Centered Care at Children's Hospital

Some of the findings from a study conducted by the Children's Hospital Research Foundation, Winnipeg, Manitoba.

1. Recognition that the family is the constant in the child's life while the service systems and personnel within those systems fluctuate

- parents identified 3 ways in which they were encouraged to feel by health care providers that they were the constant in their child's life: by a relationship of partnership with health care providers, by having real input into medical decisions affecting their child, and by having control over the level of participation in care during their child's hospitalization

- parents whose children had been diagnosed for a greater period of time (7-12 years) expected greater control and partnership in their children's health care than those that were newer to the system (less than 1 year to 3 years)

- parents felt that respect in their ability to care for their children and partnership with health care providers grew over time as each party learned to work together

2. Facilitation of parent/professional collaboration at all levels of health care

- effective collaboration is guided by trust, relationship and good conflict management. Most parents felt that this was achieved in their relationships with health care providers

- parental participation in meetings other than those related to the diagnosis or discharge from hospital were not the norm among the group interviewed

- some parents felt that they should have more participation in meetings about their child, others relied on staff to interpret the information from meetings for them

3. Sharing of unbiased and complete information with parents about their child's care on an ongoing basis in an appropriate and supportive manner

- parents felt that the information they received from health care providers about their child's condition was available, thorough and patiently delivered

- health care providers were seen by parents as being in control of the information they gave by not actively encouraging the exploration of other sources of information

- many parents believed that they should have access to the child's medical record. Lack of access caused some suspicion about what was being written and an imbalance in the relationship between parents and providers

4. Implementation of appropriate policies and programs that are comprehensive and provide emotional and financial support to meet the needs of families

- parents were not aware that formal counseling services were available to them unless they worked with teams where a mental health professional social worker, chaplain) would routinely make contact with them

Parents felt that respect in their ability to care for their children and partnership with health care providers grew over time as each party learned to work together.

- a high degree of satisfaction was expressed about the facility itself and its ability to help parents feel at home. The exception was lack of access to kitchens on the wards, expensive parking and noise at night

- providers attempt to coordinate appointments, admissions and discharges with families' personal demands within the confines of hospital organization

5. Recognition of family strengths and individuality and respect for different methods of coping

- parents generally felt respected by health care providers with whom they worked closely, and over a period of time

- respect was not automatically experienced by parents when interacting with new or different providers

- some experienced feeling judged, particularly during hospital admissions: this finding leads to speculation that hospital admissions, already stressful events, place parents and providers in a more intimate relationship, thereby raising opportunity for judgements by either party to arise

6. Understanding and, incorporating the developmental and emotional needs of infants, children, adolescents, and their families into the health care delivery system

- parents felt the providers showed genuine caring and respect for their children, and understood their unique developmental needs

- the non-medical programs such as the in-house TV, playroom and clown were applauded

- frustration was expressed by some about how hospital routines and procedures interfere with normal daily living for children in hospital

7. Encouragement of parent to parent support

- parents indicated an interest in meeting other parents in similar situations to be both helped by them and helpers to them

- health care providers do not routinely link parents with each other, thereby neglecting a possible resource for families

Recommendations

Although family-centered care is the stated philosophy of Children's Hospital, not all the principles are uniformly implemented, not all staff uniformly implement the principles, nor do all families have the same expectations of what family-centered care entails. The following are recommendations that arose from the parents in this study:

- providers should negotiate with parents what level of participation they

would feel comfortable with each time their child is hospitalized

-when dealing with parents of children with special needs, occasional and intermittent health care providers (ER, trainees, consultants, ward staff) should be particularly mindful of their brief involvement with the family

-collaboration between parents and providers could be strengthened by greater participation in meetings about the child's treatment

-regularly scheduled meetings to provide an update on the child's condition and treatment should be considered as a compliment to the ongoing information sharing that already occurs

-contact with other parents in similar situations should be routinely offered and facilitated by providers

-the use of mental health professionals should be considered to provide support to families, especially where there is no such service as an integral part of the health care team

-sleeping and kitchen facilities for parents rooming in with their child in hospital should be improved

Editor's Note: We have received hundreds of letters and e-mail messages identifying the need for information on "coping methods". We welcome your submissions for our next newsletter.

Ask the Doctor

Dr. Bonnie Cham

Question: Our child has been diagnosed with congenital Neutropenia. There is no history of this disorder in our family. How can it be congenital and what is the risk in future pregnancies?

Answer: (Dr. Bonnie Cham) The precise genetic defect underlying congenital Neutropenia is not known. In fact, there is probably more than one form of congenital Neutropenia. It is not uncommon for a child to be diagnosed with this disorder without a family history. This may be for several reasons.

Some forms of congenital Neutropenia are inherited in an autosomal recessive manner. This means that each parent has one gene which is affected and one which is not. In order to have Neutropenia, both genes must be affected and so although the parents are both healthy, the child who inherits both affected genes (one from each parent) has Neutropenia.

Congenital Neutropenia may also be inherited in an "autosomal dominant fashion with variable penetrance". This means that although only one copy of the affected gene may be needed to be neutropenic, not all people who have the affected gene are equally affected.

Finally, it is possible for a new mutation to arise in the development of a fetus such that the infant is neutropenic, and may be able to pass the Neutropenia gene.

Unfortunately, we do not have the ability yet to determine exactly where the genes are which result in congenital Neutropenia. In most cases, there is no genetic testing which can be done to predict whether future offspring will be affected. In the absence of a positive family history however the chances are fairly low that your next child will be affected. You should be sure however to discuss this with your doctor, as there may be information specific to your child's case which would be helpful in determining the risk.

Question: Have you heard of Neutropenia being misdiagnosed or somehow related to ITP?

Answer: (Dr. Bonnie Cham) ITP refers to a disorder where platelets are destroyed by an antibody made by the patient which reacts against the platelets.

This antibody production often follows a viral infection as part of the immune response.

In children it is usually self-limited although treatment may be required to maintain the platelet count at a safe level until the body overcomes the antibody problem.

Neutropenia may also occur in children following a viral infection and is known as autoimmune Neutropenia. This disorder is also related to an antibody and is usually self-limited in young children (although may last for 6 - 24 months). Usually symptomatic management is all that is necessary however in patients with significant infectious problems, G-CSF has also been used with some success.

Question: We are looking for information on hypogammaglobulinemia with Neutropenia or Neutropenia. We have a history of the above mentioned disorder in our family and presently have a four year old nephew who has been stricken with this disorder. We are trying to get information so that we can send it to his doctors who can possibly help resolve his problem.

Also, if you have any information on the newly founded procedure of stem cells from umbilical cords, we would like to hear your input. We are not necessarily technical regarding the language or the medical information we are requesting; however, we are hoping that you may enlighten us on this matter.

Answer: (Dr. Bonnie Cham) The procedure being referred to is a stem cell transplant (similar to bone marrow transplant).

It is being done, in certain centers and

on experimental protocols, to be able to perform bone marrow transplants from unrelated donors for patients in whom a bone marrow transplant is indicated but no family donor is available.

The advantages of umbilical cord rather than the regular unrelated registry from adult volunteer donors relates to the observation that there is less graft versus host disease when the donor of the marrow is younger. Because of this, in some centers, these transplants are being performed when there is less similarity between the HLA types than normally required. Because of this, a donor may be easier to find (i.e. doesn't always need to be a perfect match.) (Again this is generally still considered experimental).

Whether the patient is a candidate for transplant would certainly depend on the severity of infections. If he is severely neutropenic, and having very significant infections despite receiving regular gammaglobulin and Neutropenia therapy, he may well be a BMT candidate.

In the US there is a cord blood bank run out of the New York Blood Center. In Canada there is a new bank being set up in Edmonton by Dr. John Akabutu in conjunction with the Red Cross. I really do not have enough information about this patient, prior therapies, or the Cord Bank policies to make a comment as to whether he is a candidate for this type of therapy. It does have the risks of a bone marrow transplant, it simply uses a source of stem cells other than bone marrow.

Question: Is cyclic Neutropenia rare for children under one year of age?

Answer: (Dr. Bonnie Cham) This disorder can occur right from birth. A review article by Dr. Dale mentions that about 1/3 of well documented cases in the literature have clinical evidence prior to their first birthday. So, although this is a rare disorder, I would certainly consider it possible at less than one year of age.

Also see.

Wright DG, Dale DC, Fauci AS, and Wolff S : Human cyclic Neutropenia: Clinical review and long-term follow-up of patients. Medicine vol 60: pp1-13 1981.

A question was raised about intermittent treatment of cyclic Neutropenia:

Answer: (Dr. Bonnie Cham) regarding intermittent G-CSF for cyclic Neutropenia. Most reports use either every other day throughout the cycle or 3 days/ week (e.g. Mon, Wed, Fri.)

However there is a report from Sweden in the European Journal of Hematology by Danielsson regarding the use of G-CSF 3 to 4 days prior to the expected count nadir and stopping as the counts rise. When they started the G-CSF at the time of the nadir, no response was seen and the infectious symptoms were not reduced. If you are going to dose only with the nadir it's probably important to start several days prior to the drop.

A question about sugar intake from a Nutritionist:

Answer: Our children gain weight poorly in early childhood. Some parents (and, frankly, even some health-care providers) believe that this is a reason to increase sugar intake. It is not unusual to hear parents who have been advised to let their kids eat any high calorie foods, even lots of candy, to get the calories into them.

The irony is that some (not all) people whose gut has been damaged by frequent loose stools can indeed be temporarily sucrose intolerant (mechanism: damaged microvilli & temporary loss of dissachradase activity). In sucrose-intolerant people, sugar leads to diarhhea (and more weight-loss). So sugar is bad advice for GI reasons as well.

Doctor To Doctor

Questions Frequently Asked by Treating Physicians

Question: What advice should be given to a patient with SCN who is receiving G-CSF and who develops a fever?Answer: Patients with SCN who are responsive to G-CSF have a lower risk of invasive bacterial infection than those patients who are untreated. However response to G-CSF can fluctuate over time and therefore it is recommended that a patient with SCN who is receiving G-CSF have a CBC performed within the first day of onset of fever. The urgency of seeking medical attention must be based on the individual patient's history of infection, response to G-CSF and any other associated symptoms at the time of onset of the fever.

It should also be noted that G-CSF is not itself a pyrogen, therefore, fever occurring during therapy with G-CSF should not be attributed to the G-CSF itself. A patient on G-CSF may develop infection despite having a good ANC. G-CSF administration should be continued during treatment of infection.

Question: How frequently should a patient be monitored with blood counts while receiving G-CSF and when should the dose be adjusted?

Answer: When initiating G-CSF treatment, the SCNIR Advisory Board recommends that one aims for an absolute neutrophil count (ANC) of 1.0 to 10 x 109/L. It is important to monitor total white blood cell count and neutrophil count at least weekly until the neutrophil count stabilizes. One then titrates the dose based on clinical response.

Data from the Registry indicates that patients with congenital Neutropenia (e.g. Kostmann's) are being treated with a median dose of 5.6 mcg/kg/day. Those patients with cyclic Neutropenia are requiring a median dose of 1.7 mcg/kg/day while patients with idiopathic Neutropenia are being treated with a median dose of 1.0 mcg/kg/day. It is important to note that patients with cyclic Neutropenia will still have a cyclical pattern to their neutrophil count despite a good response so there may be quite a wide variation in ANC between troughs and peaks.

Once individuals are stabilized on G-CSF therapy, monthly monitoring of ANC during the first year of therapy is recommended. G-CSF dosage may need to be adjusted if there are very high or very low counts obtained. Blood samples should be drawn prior to the daily administration of G-CSF In our practice, we have found that after the first year of therapy, providing the patient is stable on G-CSF treatment, blood counts may be obtained less frequently (possibly every two to three months).

The aim of G-CSF therapy is to improve the ANC and ameliorate symptoms associated with the Neutropenia. The goal is to maintain the patient on the lowest dose of G-CSF necessary to maintain sustained relief of symptoms. Providing the patient is well, G-CSF treatment may be reduced to alternate day administration or occasionally even less frequently.

Excerpts from the Fall 1996, and Spring 1997 SCNIR News Update

SCN at ASH '96

This newsletter will focus on recent advancements in the understanding of severe chronic Neutropenia and its therapy. At the American Society for Hematology meeting in Orlando Florida, Dec 6-10, 1996 there were several papers of interest.

The SCNIR Advisory Board presented three abstracts regarding information arising from the Registry. Additional papers were presented by board members and their collaborators regarding their own independent research.

Dr. Mel Freedman, chair of the Safety Review subcommittee of the SCNIR advisory board, presented a current paper entitled "MDS/AML in patients with severe chronic Neutropenia (SCN) receiving G-CSF". This is an adverse outcome of SCN which has previously been reported both by the registry and others. The data presented indicated that this outcome has been exclusively seen (to date) in patients with congenital Neutropenia as opposed to cyclic or idiopathic patients. No relationship between dose or duration of G-CSF therapy is apparent. Abnormalities in G-CSF-Receptor proteins have been found to develop in some patients, along with acquisition of a ras oncogene mutation and development of acquired monosomy 7 in marrow stem cells. These abnormalities have not been found to be present at onset of G-CSF therapy, meaning that they are not related to the etiology of the Neutropenia. However, their development during therapy raises questions as to whether these patients, who are thought to have a predisposition to leukemia based on their underlying disorder, are now living long enough due to supportive care to develop leukemia, or whether the G-CSF is accelerating this conversion.

The outcomes of the patients who have developed MDS/AML while on G-CSF therapy were also reviewed. The only survivors are those who have had bone marrow transplants. Even in the transplanted group, there has been a high mortality (75%), at least partially related to advanced disease at the time of transplant. It is with this in mind that the Registry continues to strongly urge physicians to obtain yearly bone marrow examinations on patients with congenital Neutropenia for routine morphology, as well as cytogenetics. For those patients who acquire a clonal cytogenetic abnormality, strong consideration should be given to bone marrow transplantation in an early stage.

Development of Leukemia and Cytogenetic Abnormalities

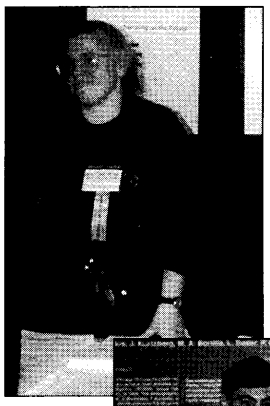
For patients with congenital Neutropenia, the development of cytogenetic abnormalities, myelodysplasia, and leukemia remain the issues of greatest concern. Cases of leukemic transformation were documented in congenital Neutropenia patients prior to the use of cytokines (DeVries et al, 1958; Gilman et al, 1970; Lui et al, 1978; Matsaniotis et al, 1966; Rosen and Kang, 1979). Of the published cases of congenital Neutropenia, 42% of patients died at a mean age of 2 years secondary to sepsis and pneumonia (Young and Alter, 1994). In the SCNIR 1995 annual report, the median age of congenital Neutropenia patients enrolled in the Registry was 10.4 years (range 0.2 to 40.6).

To date, Registry reports of leukemic transformations have occurred only in the congenital Neutropenia patients; no leukemic transformations have occurred among patients with cyclic or idiopathic Neutropenia. Among the 191 congenital Neutropenia patients from the clinical trials, with an average follow-up of 4.7 years, 22 have been reported to develop AML/MDS. The rate of MDS and AML reported in these congenital Neutropenia patients in the SCNIR who were treated with NEUPOGEN for up to 5 years is 1.6 cases per 100 patient-years of exposure; for patients with acquired types of SCN (cyclic and idiopathic), this rate is zero cases per 100 patient-years of exposure.

Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with NEUPOGEN who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, myelodysplasia, or acute leukemia is related to chronic daily NEUPOGEN administration or to the natural history of SCN. The SCNIR has recommended annual bone marrow and cytogenetic evaluation in all patients with congenital Neutropenia.

The Registry is extremely interested in collecting a bone marrow sample for preservation by freezing from all patients with congenital Neutropenia and cyclic Neutropenia. The best sample is the sample obtained before treatment, however, for patients already on therapy, we are interested in obtaining bone marrow cells from the next bone marrow aspirate performed. These samples will be invaluable for long-term laboratory studies in these patients. We are in the process of establishing a cell bank in each continent for this purpose. Please call your DCC office for further information.

Lorna Stevens & Dr. Connie Zeidler (below) Audrey Anna Bolyard, SCNIR Clinical Manager



Dr. George Kannourakis and Dr. Karl Welte, 1996 ASH presentation

Severe Chronic Neutropenia International Registry (SCNIR)

This international disease registry was established in March, 1994, and is directed by an advisory board of physicians who treat SCN patients. The mission of this registry is to establish a worldwide database of treatment and disease related outcomes for persons diagnosed with SCN. The information collected will lead to improved medical care and become a focus for future research.

* Severe Chronic Neutropenia
* Cyclic Neutropenia
* Idiopathic Neutropenia
* Autoimmune Neutropenia

For more information, contact:
Audrey Anna Bolyard

U.S.: 1-800-726-4463

CAN: 1-206-543-9749

or write:
SCNIR
Puget Sound Plaza
1325 4th Ave, Suite 620
Seattle, WA 98101-2509
USA

E-mail:
registry@u.washington.edu

The SCN Registry is supported by Amgen, Inc.

If you would like to be on our mailing list, please fill out the form below

Name _____

_____

Address _____

_____

_____

City _____

State/Prov. _____

Zip/Postal Code _____

Phone _____

Mail to: Audrey Anna Bolyard, SCNIR, 1325 4th Avenue, Suite: 620, Seattle, WA 98101-2509

SCNIR Advisory Board Members

Dr. Mary Ann Bonilla
St. Barnabas Medical Centre
101 Old Short Hills Road
Suite 400-A West Orange,
New Jersey 07052
Tel. (201) 325-6700
Fax. (201) 243-6253

Dr. Laurence A. Boxer
University of Michigan
Women's Hospital
Room L 2110
1500 E. Medical Center Drive
Ann Arbor, MI 48109-0238
Tel: (313) 764-7126
Fax: (313) 936-8520

Dr. Patricia Catalano
Amgen
3200 Walnut Street
Boulder, CO 80301
Tel: (303) 541-1421
Fax: (303) 938-6246

Dr. Bonnie Cham
Manitoba Cancer Treatment and Research Foundation
100 Olivia Street
Winnipeg, Manitoba
Canada R3E 0V9
Tel: (204) 787-2188, ext. 4147
Fax: (204) 783-6875

Director: Dr. David C. Dale
University of Washington
1959 N. E. Pacific Street
Department of Medicine
Box 356422
Seattle, WA 98195-6422
Tel: (206) 543-7215
Fax: (206) 685-4458

Dr. Melvin Freedman
Hospital for Sick Children
555 University Avenue
Toronto, Ontario
Canada M5G 1X8
Tel: (416) 813-6152
Fax: (416) 813-5327

Dr. George Kannourakis
Cancer Research Centre
University of Ballarat
St. John of God Hospital
1002 Mair Street
Ballarat, Victoria, Australia
Tel: 61-53-33-4811
Fax: 61-53-33-4813

Dr. Sally Kinsey
Consultant Paediatric Haematologist
Children's Day Hospital
St. James's University Hospital
Beckett Street
Leeds LS9 7TF, UK
Tel: 44 113 283 7014
Fax: 44 113 247 0248

Professor Pier Giorgio Mori
IV Divisione Pediatria
Ematologia ed Oncologia
Istituto Giannina Gaslini
16148 Genova Ouarto
Genova, Italy
Tel: 00 39 10 5636556
Fax: 00 39 10 3776590

Professor Karl Welte
Kinderklinik
Medizinische Hochschule
Konstanty Gutschow Str 8
30623 Hannover Germany
Tel: 00 49 511 532 9020
Fax: 00 49 511 532 9120

Contacts

Audrey Anna Bolyard, RN, BS
Clinical Manager

Tammy Cottle
Data Manager

University of Washington
SCNIR
Puget Sound Plaza
1325 4th Ave. Suite 620
Seattle WA 98101-2509
Phone: 1-800-726-4463 or
206-543-9749
Fax: 206-543-3668

Cornelia Zeidler, MD
Clinical Manager

Kristine Crusius
Data Manager

SCNIR
The Medical Park
Feodor-Lynen-Str27
30625 Hannover, Germany

Phone: 0 1 1-49-511-546-0918
Fax: 01 1-49-511-546-0919

SCNIR European Local Liaison Physicians

LUXEMBOURG

Dr Caroline Duhem
Department of Hemato-Oncology
Centre Hospitalier du Luxembourg
rue E. Barble 4
L-1210 LUXEMBOURG
Tel: 00 352 44 11 20 84
Fax. 00 352 45 87 62

NETHERLANDS

Dr Marie C A Bruin
Het Wilhelmina Kinderziekenhuis
Afdeling Kindergeneeskunde
Nieuwegracht 137
3512 LK UTRECHT
THE NETHERLANDS
Tel: 00 31 30 2 320 711
Fax: 00 31 30 2 34 825

Dr A Y N Schouten-van Meeteren
Academisch Ziekenhuis Vrije Universiteit
Afdeling Kindergeneeskunde
De Boelelaan 1117
1081 HV AMSTERDAM
THE NETHERLANDS
Tel: 00 31 20 4442419 / 4442420
Fax: 00 31 20 4442422

Dr Gert J Ossenkoppele
Academisch Ziekenhuis Vrije Universiteit
Afdeling Inteme Geneeskunde
De Boelelaan 1117
1081 HV AMSTERDAM
THE NETHERLANDS
Tel: 00 31 20 444 2604
Fax: 00 31 20 444 4645

SPAIN

Dr Juan J Ortega Aramburu
Head of Hematology Dept.
Hospital Universitari Matemo-Infantil Vall d'Hebron
Pg Vall d'Hebron, 119-129
08035 - BARCELONA
SPAIN
Tel: 00 34 3 427 20 00 ext 2313
Fax: 00 34 3 428 21 71

Dr Evaristo Feliu Frasnedo
Head of Hematology Department
Hospital Germans Trias i Pujol
Ctra. del Canyet, s/n.
08916 - Badalona
BARCELONA
SPAIN
Tel: 00 34 3 465 12 00
Fax: 00 34 3 395 4206

SWEDEN

Professor Jan Palmblad
Consultant Haematologist
Medicinkliniken
Soersjukhuset
11883 STOCKHOLM
SWEDEN
Tel: 00 46 8 616 32 68
Fax: 00 46 8 616 32 17

UK

Dr Jane Evans
Consultant Haematologist
The Hospital for Sick Children
Great Ormond Street
LONDON
UK
WCIN 3JH
Tel: 00 44 171 829 5379
Fax: 00 44 171 430 1600

Dr Sally Kinsey
Consultant Paediatric Haematologist Children's Day Hospital
St James's University Hospital Beckett Street
LEEDS
LS9 4TF
UK
Tel: 00 44 113 283 7014
Fax: 00 44 113 247 0248

BELGIUM

Dr Andries Louwagie
Head of Hematology Department A.Z. Sint Jan
Ruddershove 10
B-8000 BRUSSELS BELGIUM
Tel: 00 32 50 45 21 11
Fax: 00 32 50 45 25 93

Dr Christiane Vermylen
Department of Pediatric Hematology U.C.L. St. Luc
Avenue Hippocrate 10
B-1200 BRUSSELS
BELGIUM
Tel: 00 32 2 764 1800
Fax: 00 32 2 764 8916

FRANCE

Dr Jean Donadieu
Service du Pr. Griscelli Hopital Necker
149 rue de Sevres
75743 PARIS CEDEX 15
Tel: 00 331 44 49 54 12
Fax: 00 331 42 73 28 96

GERMANY

Dr Gundula Notheis
Immundefekt-Ambulanz
der Universitats-Kinderklinik
Lindwurmstr. 4
80337 MUNICH
GERMANY
Tel: 00 49 89 51 60 28 11
Fax: 00 49 89 51 60 47 25

Director Professor Karl Welte
Dr. Connie Zeidler
sche Hochschule
Kinderklinik
30623 HANNOVER
GERMANY
Tel: 00 49 511 532 9020
Fax: 00 49 511 532 9120

IRELAND, REPUBLIC OF

Dr Owen Smith
Consultant Haematologist
St. James Hospital
Dublin 8
Ireland
Tel. 00 3531 453 7941 (x2014
Mobile Phone: 0885 18369

The National Children's Hospital
Harcourt Street
Dublin 2
Ireland
Tel: 00 353 1 475 2355
Fax: 00 35 31 475 8501

ISRAEL

Professor Yigal Barak
Kaplan Hospital
Department of Pediatrics A and Pediatric Hematology-Oncology
Jemsalem
Rehevot
76100
ISRAEL
Tel: 00 972 (08) 944 1276/9
Fax: 00 972 (08) 941 1942

ITALY

Professor Pier Giorgio Mori
IV Divisione Pediatria
Ematologia ed Oncologia
Istituto Giannina Gaslini
16148 Genova Quarto
GENOA
ITALY
Tel: 00 39 10 5636556
Fax: 00 39 10 3776590

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!

Recommended Reading!

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.

FILGRASTIM (r-metHuG-CSF) IN CLINICAL PRACTICE

edited by George Morstyn. T. Micheal Dexter. Price: $125.00 (U.S.)

To Order: Call 1-800-228-1160
Or Write to:
Marcel Dekker Inc.
270 Madison Ave. New York,
N.Y. U.S.A. 10016

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

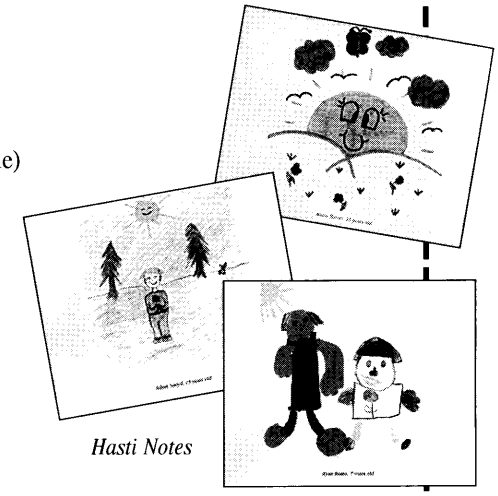
SEND TO:

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" (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) (as available)
_____ copies of Chemotherapy and Neutropenia (French) (as available)
_____ Video tape — Physician Presentations
_____ Video tape — Physician presentations "in layman's terms"
_____ Update mailing information only
_____ "Caring Cards" Hasti Notes #_____ (6 for $5.00)



Hasti Notes

NAME: _____

ADDRESS: _____ CITY: _____

PROVINCE/STATE: _____ COUNTRY: _____

POSTAL/ZIP CODE: _____ PHONE NUMBER: _____

For Hospital/Medical Centre/Health Care Professionals please add:

ATTENTION: _____ *WARD/UNIT:* _____

WE SUPPLY THIS INFORMATION FREE OF CHARGE

Use this handy form to send in your tax deductible donations

Individual and family $10.00 ☐

Business or Corporate $25.00 ☐

New ☐ Renewal ☐ (CHECK ONE)

All donations gratefully received.

NAME _____

ADDRESS _____

CITY/PROV. _____

POSTAL/ZIP CODE _____

PHONE# _____

Send to Neutropenia Support Assoc. Inc. P.O. Box 243, 905 Corydon Ave. Winnipeg, Manitoba R3M 3S7

Help us distribute information! Please recycle your newsletter by sending it to your physician or local health care centre. Thank you!