

# **UNDERSTANDING SEVERE CHRONIC NEUTROPENIA**

**A handbook for patients and their families**

Written for the  
**Severe Chronic Neutropenia International Registry**  
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## INTRODUCTION

Severe chronic neutropenia (SCN) is the name given to a group of conditions in which neutropenia is the primary problem. The severity and symptoms of the neutropenia differ widely among the various sub-types of neutropenia and even from patient to patient within each disease type. This handbook is designed to give you a better understanding of SCN. It has been written to answer many of the questions you may have about neutropenia and treatment for it. We hope that you find it useful in helping you and/or your child in coping with the disease. The purpose of this document is to give you information and to empower you to go back and ask questions to your physician. There is an ongoing process of investigation and research into severe chronic neutropenia and its management. Consequently, this handbook is not all-inclusive and further updates may be obtained from the registry web site.

The staff members of the Severe Chronic Neutropenia International Registry (SCNIR) wrote this handbook. The SCNIR was established in 1994 under the sponsorship of Amgen Inc., Thousand Oaks, CA, USA. On July 1<sup>st</sup>, 2000, the SCNIR has become an independent organisation dedicated to research and education in chronic neutropenias. We would like to thank the Advisory Board members of the Registry for their contributions and also, Debra Scarlata and Carol Fier of Amgen Inc. for reviewing the contents.

For the purpose of this document "you" refers to you/your child.

Throughout the text there are words and phrases that appear in *Italics*, these are explained further in the glossary on page 43ff.

## HOW BLOOD IS FORMED

The *bone marrow* is where all blood cell production takes place.

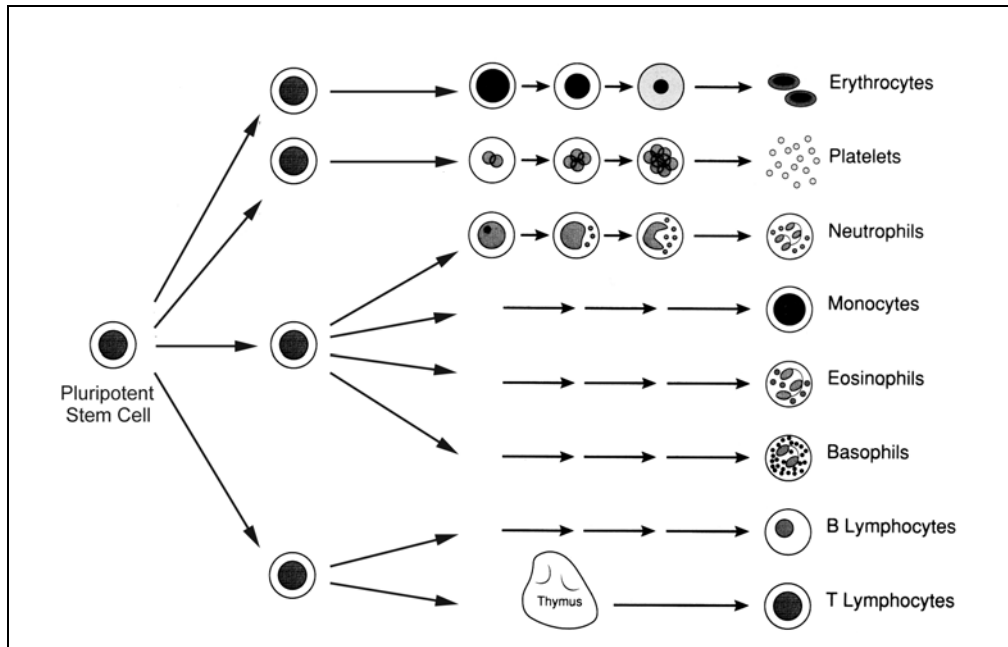
The *bone marrow*, as its name indicates, is located within the bones. The skeleton of the adult human body is built of different types of bones. The bones of arms and legs are long bones with an inner cavity housing mainly fatty tissues, nerves and blood vessels. The marrow in the long bones is of yellow colour and because of its fat content is referred to as yellow or fat marrow. This yellow marrow is not actively involved in the production of blood cells in an adult.

The red, blood-forming marrow is located within a different type of bone that is flat like the breastbone and the pelvic bone. These bones are not hollow inside but contain a sponge-like scaffolding made from bone substance. The gaps in-between the bone structures are filled with little nests of blood-forming cells, supporting cells and a network of nerves and small nourishing blood vessels. The medical term for the formation of blood cells is *haematopoiesis* (see figure 1).

There are three basic types of blood cells:

- The red blood cells (*erythrocytes*) carry oxygen from the lungs to all the tissues of the body
- The *platelets* (*thrombocytes*) are essential for the clotting of the blood
- The *white blood cells* (*leukocytes*) are in charge of the body's defence against infections. There are three main types of *white*

*blood cells: granulocytes, monocytes, and lymphocytes. Neutrophils make up the major part of the granulocytes.*



**Figure 1.** All types of blood cells shown in the bottom line are derived from one single ‘mother cell’, the so-called *pluripotent haematopoietic stem cell*.

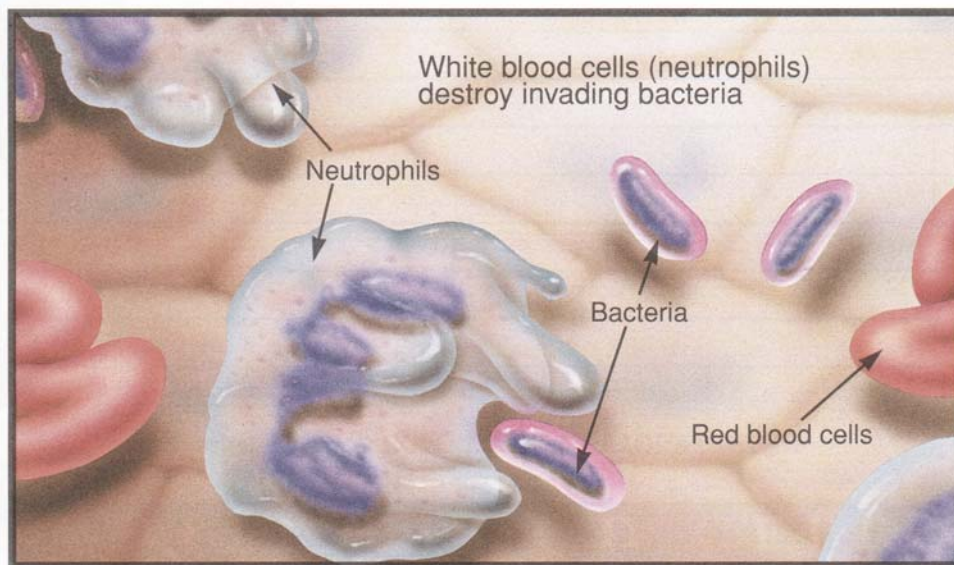
The growth and development of the blood is carefully controlled in the *bone marrow* to produce the correct number of each type of cell to keep the body healthy. About 3 million red and 120 thousand *white blood cells* are produced every second. The mature cells leave the *bone marrow* and enter the blood stream and circulate with the blood through the body. All different blood cells are derived from a single type of cell called the *stem cell*. Only a very small proportion of *bone marrow* and blood cells are *stem cells*. These are the cells that need to be collected for *stem cell* or *bone marrow* transplantation (BMT) (see page 23)

All blood cells eventually die but their life spans vary amongst the different types of cells. Red blood cells live for about four months

after they leave the *bone marrow*, whereas *platelets* live for just a few days and *granulocytes (neutrophils)* for only a few hours.

## WHAT IS NEUTROPENIA?

The term neutropenia describes the situation where the number of *neutrophils* in the blood is too low. *Neutrophils* are very important in defending the body against bacterial infections (see figure 2) and therefore, a patient with too few *neutrophils* is more susceptible to bacterial infections. Neutropenia can occur for different reasons. Patients who have cancer may become neutropenic because of the *chemotherapy* they receive, sometimes neutropenia occurs after a viral infection. Some people are born with neutropenia, but in some cases the reasons are not known.



**Figure 2.** Watching the blood stream ‘through a window’ in the wall of a blood vessel.

The level of neutropenia may vary considerably. In general, the blood of healthy adults contains about 1500 to 7000 *neutrophils* per  $\text{mm}^3$  ( $1.5 - 7.0 \times 10^9/\text{l}$ ). In children under 6 years of age the neutrophil count may be lower. The severity of neutropenia generally depends on the absolute neutrophil count (*ANC*) and is described as follows:

- Mild neutropenia, when the *ANC* falls below a lower limit of 1500 per  $\text{mm}^3$  ( $1.5 \times 10^9/\text{l}$ ), but remains higher than 1000 per  $\text{mm}^3$  ( $1.0 \times 10^9/\text{l}$ )
- Moderate neutropenia, when the *ANC* falls between 500 per  $\text{mm}^3$  and 1000 per  $\text{mm}^3$  ( $0.5 \times 10^9/\text{l} - 1.0 \times 10^9/\text{l}$ )
- Severe neutropenia, when the *ANC* falls below 500 per  $\text{mm}^3$  ( $0.5 \times 10^9/\text{l}$ )

The duration of the neutropenia may be short lived. In short-lived cases, the patient is described as suffering from acute neutropenia. However, if a patient has neutropenia for a longer period, i.e. greater than three months, the patient is described as suffering from chronic neutropenia.

Symptoms which patients experience depend on the level of neutropenia. The lower the neutrophil count, the greater the risk of infection. This risk increases if low neutrophil counts persist for more than three days. Types of infection include otitis media; tonsillitis; sore throat; mouth ulcers; gum infection and skin abscesses. Any fever (body temperature above  $38.5^\circ\text{C}/101.3^\circ\text{F}$ ) must be taken very seriously and your nurse or physician should be informed.

Severe neutropenia can lead to serious problems, which require prompt care and attention as the patient could potentially develop a bacterial, fungal or mixed infection at any time. These infections



can be life threatening when the patient is persistently severe neutropenic and it is therefore important that if the patient develops any signs or symptoms of an infection, then he or she should be seen by a doctor as soon as possible and treated with medications to fight the infection (such as antibiotics).

## **TYPES OF SEVERE CHRONIC NEUTROPENIA**

Severe chronic neutropenia can exist from birth (*congenital neutropenia*) or can occur at any time through life (*acquired neutropenia*). It may develop by itself or as an accompanying symptom of a different underlying disease. The following list gives you examples of the different types of chronic neutropenias.

- Neutropenias present at birth:

- Severe congenital neutropenia (*Kostmann syndrome*)
  - Cyclic neutropenia

- *Metabolic* diseases associated with neutropenia

- Shwachman-Diamond *syndrome*
  - Glycogen-storage disease type 1b

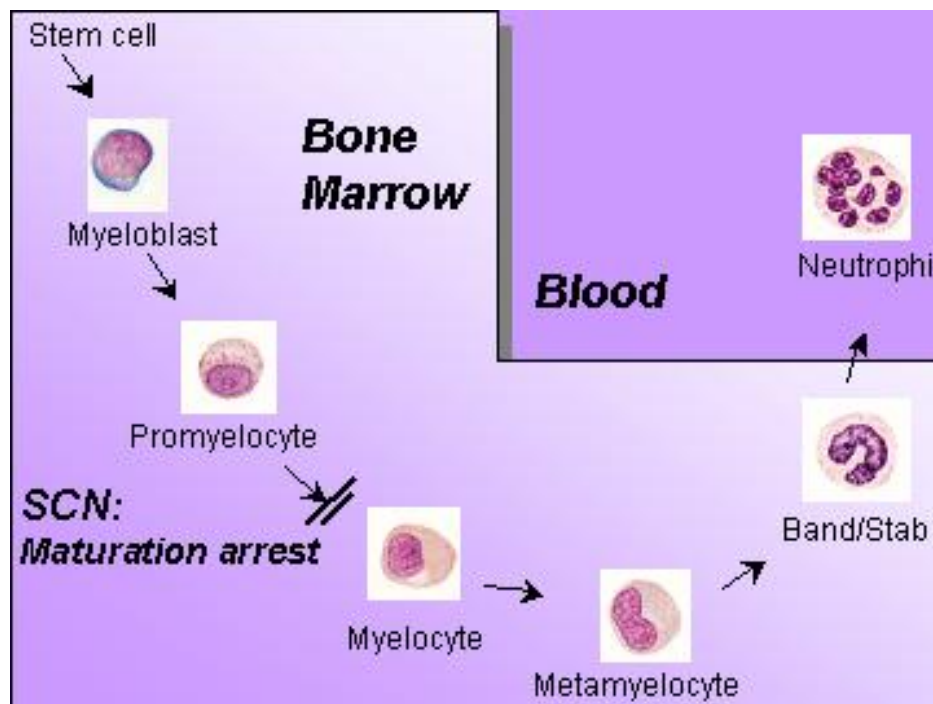
- Neutropenias that are acquired during life

- Idiopathic neutropenia
  - Autoimmune neutropenia

The different types of neutropenia are described in more detail below.

## SEVERE CONGENITAL NEUTROPENIA OR KOSTMANN SYNDROME

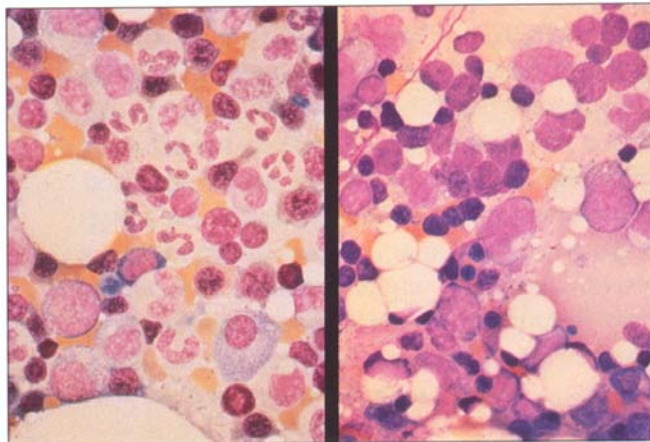
Congenital neutropenia, often also called Kostmann *syndrome* is a rare type of neutropenia that is present at birth. It is an inherited disease and therefore, more than one family member can be affected, but sporadic occurrence with only one patient in a family is also possible. However, there is no antenatal testing currently available. Congenital neutropenia is usually very severe, and *neutrophils* are often completely absent in the blood of these patients at the time of diagnosis. Patients who are diagnosed with congenital neutropenia or Kostmann *syndrome* usually show what is known as a maturation arrest (see figure 3) in the early stages of neutrophil development in the *bone marrow*. This means that their *neutrophils* rarely fully mature into the cells that are capable of fighting infections.



**Figure 3.** In healthy individuals, the maturation of neutrophilic *granulocytes* leads to segmented *neutrophils*, which leave the *bone marrow* and enter the blood. In Kostmann patients the maturation pathway is blocked at the stage of early precursor cells, the *promyelocytes*.

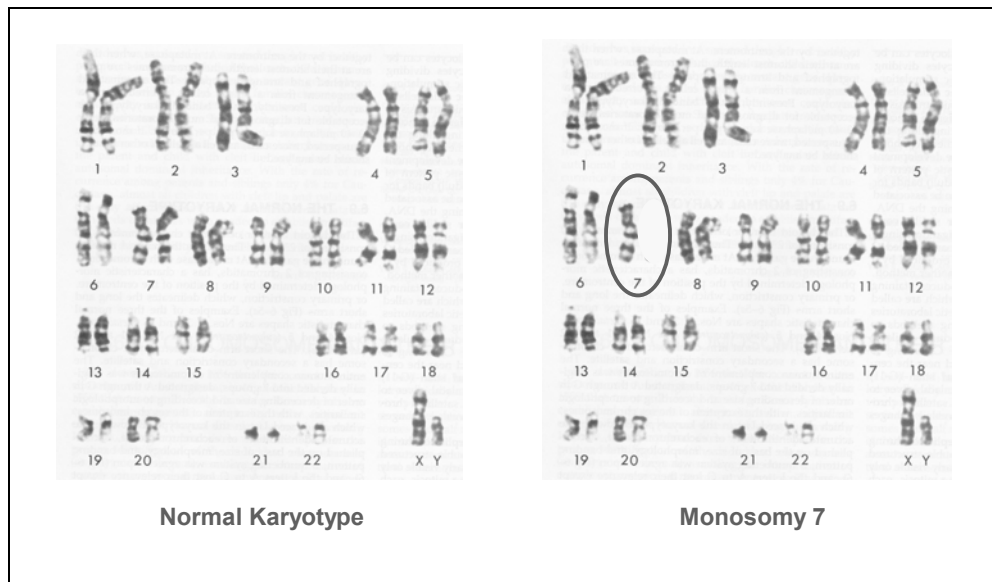
These patients suffer from severe bacterial infections, such as omphalitis (infection of the navel), pneumonia, skin abscesses or otitis media (ear infections) during their first few months of life. Therefore, in most patients congenital neutropenia is diagnosed early during infancy. A blood test and a *bone marrow* sample are required in order to obtain a correct diagnosis (see chapter **DIAGNOSIS OF SEVERE CHRONIC NEUTROPENIA** on page 17ff).

When a *bone marrow* is taken for diagnostic reasons, firstly the cells are looked at under the microscope (see figure 4) and secondly the cells are used for other investigations, such as *cytogenetic evaluation*, analysis of the *G-CSF* (*granulocyte-colony stimulating factor*) *receptor* and, if possible, a sample is sent to the SCNIR *bone marrow cell bank* to be used for research purposes.



**Figure 4.** A typical *bone marrow* of a patient with severe congenital neutropenia showing the absence of mature *neutrophils* (right) compared to the *bone marrow* of a healthy individual with *neutrophils* at all stages of maturation (left).

With the *cytogenetic* evaluation the *chromosomes* of the *bone marrow* are studied. Most of the time, in the majority of patients with neutropenia, this test is **completely normal**. Changes in the *chromosomes* of cells can be harmless, but in some cases changes could indicate a possible progression towards *leukaemia* (see figure 5). This is the most important reason for routine annual *bone marrow* investigations.



**Figure 5.** Each human cell (except for oocytes and sperms) contains two sets of 22 *chromosomes* and two additional sex *chromosomes* (females: XX, males: XY) as shown on the left side of this figure. Pre-leukaemic changes may be represented e.g. by the loss of certain *chromosomes* leading, for example, to monosomy 7 as shown on the right side of the above picture.

The analysis of the *G-CSF receptor* gives us information on the structure of this receptor. The receptor is localised on all *granulocytes*. The purpose of this particular receptor is the binding of the cytokine *G-CSF* in order to give a signal to the cell to mature, to divide itself or to enhance function. In some congenital neutropenia patients the *G-CSF receptor* develops changes that also could indicate progression towards *leukaemia*

and therefore this analysis is another sensitive indicator that needs to be tested on a regular basis.

As soon as congenital neutropenia is diagnosed, patients should commence treatment with a *haematopoietic growth factor* called *G-CSF* (also known as *filgrastim* or *lenograstim*). Clinical trials of *G-CSF* treatment began at Amgen in 1987. This treatment was found to result in a dramatic increase in life expectancy and quality of life in these patients. As soon as the patient's neutrophil counts have improved and stabilised, a near normal life can be lead e.g. going to Kindergarten or school, participation in sports. Before *G-CSF* was available, most patients died from severe bacterial infections within their first few years of life because no other treatment was able to correct their neutropenia adequately. Even antibiotic therapy could only prolong the life of these patients for a short while, because both *neutrophils* and antibiotics are necessary to overcome bacterial infections. The only option for a complete cure of *Kostmann syndrome* is a *bone marrow* transplant (BMT).

*G-CSF* is a natural cytokine produced by the human body. A cytokine is a protein produced by cells, which are essential for the regulation of other cells. Patients with congenital neutropenia also produce *G-CSF*, but for reasons still largely unknown, the response of their *neutrophils* to the normal amounts of *G-CSF* in the blood is reduced. The lower the neutrophil count, the greater the risk of infection. Occurrence of severe bacterial infections is strongly correlated with low neutrophil counts. In most patients bacterial infections resolve and reoccur less frequently as soon as the neutrophil count stabilises after initiation of *G-CSF* treatment at around  $1000/\text{mm}^3$  ( $1.0 \times 10^9/\text{l}$ ). Individual people vary, some will fight off infection with a lower neutrophil count, and others will need a higher count.

In congenital neutropenia patients, response to *G-CSF* treatment is also different. This is why there is a big variation in the dose (amount) of *G-CSF* that different people receive. For more information regarding *G-CSF* see chapter **TREATMENT FOR SEVERE CHRONIC NEUTROPENIA** on page 20ff. Only a very small subgroup of patients with congenital neutropenia does not respond to even very high doses of *G-CSF*. In patients, who do not respond to *G-CSF* doses of 100 mcg/kg or more within fourteen days, a search for a *bone marrow* donor should be started immediately and BMT should be performed as soon as a matching donor is identified. The BMT procedure is very complex: for more information contact your physician.

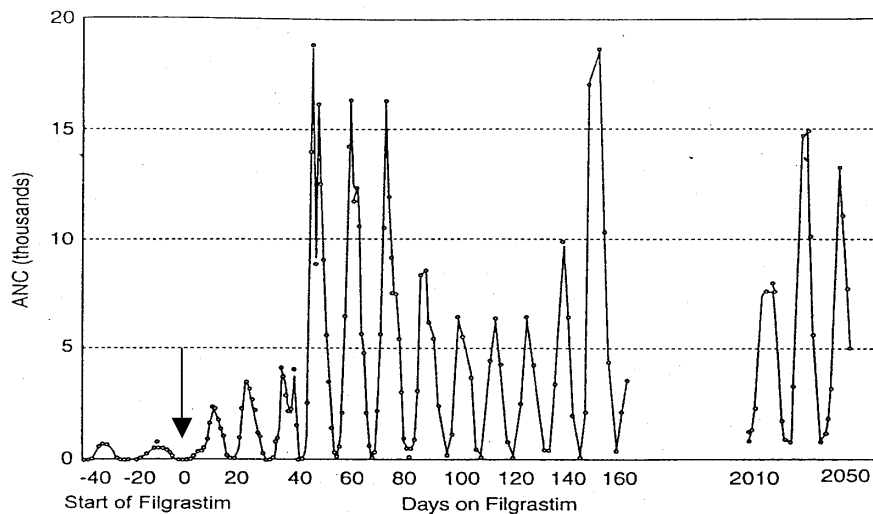
During the last 10 years, data has been collected on more than 700 patients with chronic neutropenia. These data indicate that patients who have severe congenital neutropenia have an increased risk (around 9%) of developing *leukaemia* compared to healthy individuals. Therefore, it is strongly recommended that all patients with congenital neutropenia have a *bone marrow* examination and *cytogenetic* analysis on a yearly basis. BMT may be considered if the *cytogenetics* in the *bone marrow* shows any specific abnormalities.

Besides neutropenia, patients with congenital neutropenia may have a reduced bone density, which can lead to *osteopenia* or *osteoporosis*, thinning of the bones (usually seen in elderly women). *Osteoporosis* may even be seen in children with severe chronic neutropenia, but the reasons for this are not clear. The changes in the mineral content of the bone (amount of calcium) possibly represent an additional symptom of the underlying genetic defect. However, according to all information currently available, only very few patients will actually experience clinical problems, such as pain and/or fractures due to their *osteoporosis*. Neither the

exact cause of *osteoporosis* is not fully known, nor are the long-term implications fully understood. Therefore it is important to monitor the patients' bone density on a regular basis to ensure the safety and well being of the patient.

## CYCLIC NEUTROPENIA

Cyclic neutropenia is another inherited type of neutropenia. As the name indicates, in this disease neutrophil counts show a cyclic pattern with a typical cycle length of 21 days. These cycles vary from patient to patient with some individuals being neutropenic during the whole cycle and others who have low neutrophil counts for only a few days and normal blood counts during the rest of the cycle (see figure 6). The frequency of bacterial infections depends on the length of the neutropenic period that the patient experiences. Those who have a longer neutropenic period within the cycle suffer more frequently from infections compared to patients who have only short neutropenic phases.



**Figure 6.** The absolute number of *neutrophils* in the blood of cyclic neutropenia patients cycles according to a typical pattern. Under *G-CSF* therapy, the cycling is still present but the cycle length and the duration of the neutropenic phase is shortened.

If infections (typically aphthous stomatitis - inflammation and ulceration of the mouth) occur frequently in approximately 3-week intervals, cyclic neutropenia should be considered and serial



*differential blood counts* need to be performed (at least 3 times per week over six weeks) to search for the typical cyclical pattern of blood *neutrophils* in this disease.

Almost all patients with clinically obvious cyclic neutropenia have periods of severe neutropenia (ANC less than 200 cells/ $\mu$ l) ( $0.2 \times 10^9/l$ ) every 3 weeks showing some symptoms with almost every cycle, but significant infections (e.g. otitis media, pneumonia and bacteraemia) usually are infrequent. Cyclic neutropenia occurs because of fluctuating rates of cell production by the *bone marrow stem cells*. In contrast to other causes for neutropenia, in this condition the marrow changes during the cycle, between normal appearance and that of severe maturation arrest of neutrophil production. The underlying genetic defect of cyclic neutropenia has recently been discovered. This might lead to new therapeutical approaches for cyclic neutropenia patients in the future.

Other blood cells, such as *platelets* or red cells can also show oscillations with a cyclical pattern. Cyclic neutropenia can occur sporadically, but there are families in which cyclic neutropenia is inherited with one parent and more than one child affected. As in *Kostmann syndrome*, patients with cyclic neutropenia also benefit from *G-CSF* treatment.

## **SHWACHMAN-DIAMOND SYNDROME**

Patients who present with increased volume and frequency of fatty stools need testing for pancreatic function to rule out Shwachman-Diamond *syndrome* (SDS).

SDS is an inherited (*autosomal recessive*) condition with multisystemic abnormalities including pancreatic insufficiency

(problems with digestion of fats in the diet resulting in large volume fatty stools), neutropenia, and short stature. At the time of diagnosis the features of SDS are extremely variable. The vast majority of patients are diagnosed in infancy, with symptoms of fatty stools and poor growth, with or without haematological abnormalities (including neutropenia), but other less common features can also be present at diagnosis. These include (extreme) short stature, skeletal abnormalities, and marked liver enlargement. SDS must be considered even if clinical symptoms of pancreatic insufficiency are absent because a significant percentage of patients develop pancreatic insufficiency later, or indeed their symptoms may have resolved prior to the recognition of neutropenia.

If neutropenia becomes severe, these patients also suffer from recurrent bacterial infections and treatment with *G-CSF* is helpful. Most *G-CSF* treated patients respond with an increase in blood *neutrophils* and reduction of infectious episodes. In SDS other blood cell numbers may also be decreased to a varying degree (potentially leading to *anaemia* and/or *thrombocytopenia*).

As already mentioned for patients with congenital neutropenia or Kostmann *syndrome*, patients with SDS have also an increased risk in developing *leukaemia* and therefore it is strongly recommended to have *bone marrow* examination with *cytogenetic* testing on a yearly basis.

## **GLYCOGEN-STORAGE DISEASE TYPE 1B**

Glycogen-storage disease type 1b is a rare *metabolic* disorder, which affects the glucose-6-phosphatase metabolism. The liver, spleen and other tissues accumulate glycogen. Patients present with

an enlarged liver and spleen, failure to thrive, kidney problems, hypoglycaemia (low blood sugar) and recurrent infections. The presence of an enlarged spleen can be associated with low red blood cells causing *anaemia* and *thrombocytopenia* whereas neutropenia is always present. Chronic neutropenia in these patients is accompanied by a defective function of the cells that are responsible for the killing of bacteria. Patients respond to treatment with *G-CSF* not only with an increase in *ANC* but also with improvement of the activity of their *neutrophils*.

## **IDIOPATHIC NEUTROPENIA**

The term ‘idiopathic neutropenia’ describes various types of neutropenia that may occur at any point in life for unknown reasons. Therefore onset of idiopathic neutropenia is possible in both, children and adults. As already described for the other types of neutropenia, frequency and severity of infections is correlated with the neutrophil counts. Neutrophil counts and clinical problems in these patients vary considerable, but in general those patients with the more severe neutropenia have more frequent infections. Most patients respond well to *G-CSF* treatment but require long-term treatment.

## **AUTOIMMUNE NEUTROPENIA**

(Presence of *neutrophil-specific antibodies*)

In neutropenic children aged 6 months to 4 years other than congenital neutropenia, presence of neutrophil-specific *antibodies* can result in increased destruction of the body's own blood *neutrophils*. This so-called autoimmune neutropenia is the most common cause for neutropenia of this age group. Although these

infants lack peripheral blood *neutrophils*, they usually do not suffer from severe bacterial infections.

In the serum of these patients *granulocyte-specific antibodies* are detectable by different immunological blood tests that can be performed in specialised laboratories. If *antibodies* against *neutrophils* are identified, the patients should be kept under medical care, but may not necessarily require treatment with antibiotics or *G-CSF*.

Depending on the frequency of infections and the neutrophil counts, *prophylaxis* with an oral antibiotic may be considered by the treating physician. In some children where severe infections occur, treatment with *G-CSF* is indicated. In most children the blood counts normalise during the first 2-3 years.

Autoimmune neutropenia is occasionally seen in young people (20 – 40 year age group) predominantly women and in this setting is often associated with other disorders or conditions.

## **OTHER CONDITIONS ASSOCIATED WITH NEUTROPENIA**

There are a number of other conditions that include neutropenia as part of the symptoms. Depending on the nature of the main condition the way the neutropenia is managed may differ from the treatment of ‘pure’ SCN described.

The main conditions that may include neutropenia are:

- Severe *Aplastic anaemia*
- Viral illnesses
- Post *chemotherapy* or radiotherapy

- Other drug-induced situations
- Fanconi *anaemia*.

There are some other very rare disorders, congenital or acquired, that may be associated with neutropenia, e.g. *myelokathexis*, Hyper IgM, or Combined Immunodeficiency.

This list may be incomplete and more information about diseases associated with neutropenia is being discovered all the time.

## **DIAGNOSIS OF SEVERE CHRONIC NEUTROPENIA**

When a diagnosis of neutropenia is suspected (e.g. with recurrent infections which may occur on a cyclical basis) physicians will begin by taking a *Complete Blood Count/Full Blood Count* and proceed to further tests if necessary. These examinations will be extended to include the *bone marrow* of the patient. The most important investigations performed are explained below.

The blood investigation, *Complete Blood Count (CBC)* or *Full Blood Count (FBC)*, is the same thing and these terms are interchangeable.

### **BLOOD COUNT MONITORING**

As already mentioned, the first investigation on suspicion of neutropenia is a *CBC/FBC*. By this procedure the neutrophil count is measured. If the neutrophil count is low it is normal to repeat the *CBC/FBC* to be certain that the neutropenia continues. In patients

with SCN the neutrophil count may vary slightly, but in contrast to cyclic neutropenia it always remains at a very low level.

Sometimes the neutrophil count can be normal because of a cyclical change, but at other times it is very low. In this case your physician may suspect cyclic neutropenia, then he/she will arrange for blood samples (*CBC/FBC*) to be taken three times per week for at least six weeks to see whether there is a regular cyclical pattern of neutrophil counts.

## **OTHER BLOOD TESTS**

Your physician will also do a blood test to exclude autoimmune neutropenia by testing for *antibodies* (see section regarding autoimmune neutropenia, page 15f).

## **BONE MARROW ASPIRATE/TREPHINE BIOPSY**

If your physician thinks from the blood tests that you have a type of neutropenia, then it is important to do a *bone marrow* examination to confirm the diagnosis by looking at the marrow cells under the microscope (see figure 4 on page 8).

*Bone marrow* cells are usually taken from the large pelvic bone, the ilium, or, sometimes also from the flat breastbone, the sternum. This is usually done with the patient asleep under general anaesthetic or under local anaesthetic with sedation. The actual technique may vary between treating centres. Your physician will explain exactly how the procedure will be done for you.

There are two different methods to examine *bone marrow*. Firstly, marrow cells can be taken out like taking a blood sample from a vein (*bone marrow* aspirate), but this time from the middle of the bone. Secondly, a small piece of the solid, bonier part of *bone marrow* is taken (*bone marrow* biopsy) and processed differently, to look at the architecture of the marrow structure.

## **CYTOGENETIC EVALUATION AND MOLECULAR TESTING**

As mentioned previously (page 11) it is important to monitor the *cytogenetics* of the marrow cells. Any *morphological* abnormality of the marrow cells may be preceded by a change in *cytogenetics*.

There are additional techniques by which some *cytogenetic* changes can be monitored; your physician will explain these to you.

SCN is a very rare disorder. Some treating centres are actively involved in research of SCN and may wish to discuss other investigations.

## **INVESTIGATIONS IN OTHER CONDITIONS**

To be certain about the diagnosis of conditions that are not limited to the blood system like Shwachman-Diamond *syndrome* (see page 13f) and Glycogen-Storage Disease (see page 14f), it will be necessary to do different investigations, in addition to blood tests. Your physician will explain what further tests are required. Sometimes this may even involve being seen by another specialist.

## TREATMENT FOR SEVERE CHRONIC NEUTROPENIA

The treatments that have been tried or are being used in the management of congenital, cyclic and idiopathic neutropenia include:

- ***Granulocyte-colony stimulating factor (G-CSF)***
- ***Bone marrow transplant (BMT)***
- **Others: including other cytokines, antibiotics, vitamins, immunosuppressive drugs, immunoglobulins, corticosteroids and white cell transfusions**
- **Supportive care**

As well as the treatment prescribed by your physician, nutrition and good hygiene, including good dental hygiene are extremely important in overall care to decrease the potential for infection. Nutritional treatments will not however raise the neutrophil count in severe chronic neutropenia.

The specific treatment for you should be discussed with your physician. These discussions should include any benefits of treatment and any potential risks.

### GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF)

*G-CSF* is a cytokine normally produced by the human body itself. *G-CSF*, which is given as treatment is NOT from human beings but is safely made by industrial processes to produce an identical substance (by *genetic engineering*) that has all the normal activity and function of the naturally occurring cytokine. Therefore there is no risk of viral infection from *G-CSF* therapy.



*G-CSF* stimulates the production and also enhances the activity of mature *neutrophils* thus improving their bacteria-killing function. It acts via a receptor localised on *granulocytes* that binds the *G-CSF* to the cell and produces a signal to mature, to divide or to enhance function (see figure 3 on page 7).

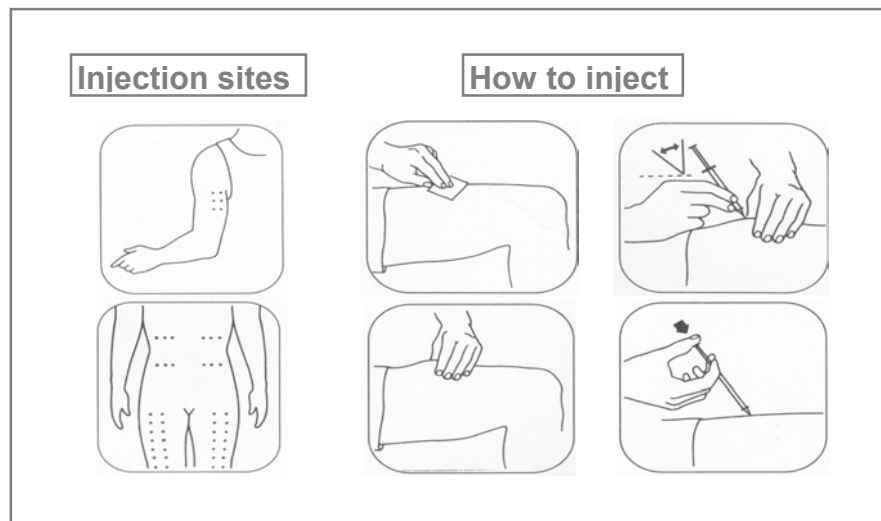
SCN patients produce their own *G-CSF*, but for unknown reasons it does not produce the normal effects within the blood system and, therefore, extra (treatment) *G-CSF* is required.

The dose and frequency of injection of *G-CSF* that is required to increase and maintain the neutrophil count to 1000 per mm<sup>3</sup> (1.0 x 10<sup>9</sup>/l) varies widely. For most patients, 5-20 micrograms (mcg) per kilogram (kg) of body weight of *G-CSF* given as a daily *subcutaneous* injection is usually sufficient but some patients need very high doses, even up to 120/mcg/kg/day (potentially applied in more than one injection per day or even by continuous i.v. infusion) and some will require very low doses, as low as 0.01 mcg/kg/day. For some patients with severe chronic neutropenia the frequency of administration of *G-CSF* may be required less than daily, but short-term amendments may be necessary if illness due to infection occurs.

*G-CSF* is usually administered by a *subcutaneous* injection (i.e. an injection just under the skin) and recommended sites include the abdomen below the naval, upper outer arms, and upper outer thighs (figure 7). It is possible to self-administer *G-CSF* and this should be encouraged as it promotes a sense of independence and control over at least one aspect of treatment. As with any frequent and regular *subcutaneous* injection, rotation of the sites is recommended to prevent scarring and discomfort to the patient. The injection is not usually painful but, occasionally, a stinging

sensation may be experienced for a short period of time on administration.

Administration of *G-CSF* may result in a dramatic increase in the numbers of *neutrophils* in the blood and is without doubt, the most effective therapy in treating SCN. Some SCN patients receiving G-



**Figure 7.** Where and how to apply *G-CSF*.

CSF report bone or muscle pain and *splenomegaly*. Other side effects are infrequent but few patients have experienced *thrombocytopenia*, injection site reactions, rash, *hepatomegaly*, *arthralgia*, *osteoporosis*, *cutaneous vasculitis*, *haematuria/proteinuria*, *alopecia* and exacerbation of some pre-existing skin disorders (e.g. *psoriasis*). If you are concerned that you may experience these or other side effects, report them to your doctor. In addition, *cytogenetic* abnormalities, transformation to *MDS* and *AML* have been observed in patients with congenital neutropenia treated with *G-CSF*. It is unknown whether the development of these abnormalities is related to chronic daily *G-CSF* administration or to the natural history of congenital neutropenia (see also page 8).

## **BONE MARROW TRANSPLANT**

BMT is a treatment option for SCN. It may be considered for failure to respond to treatment, or for patients who develop *leukaemia* or *MDS* in the course of their disease. BMT is a very intensive procedure, carrying serious risks and therefore it is not recommended as first choice treatment. Your physician will be able to discuss this with you.

## **OTHERS TREATMENTS**

### **Corticosteroids**

In some conditions steroids have long been effective at increasing neutrophil counts in the blood. Steroids work by encouraging *neutrophils* to leave the *bone marrow* and enter the blood stream. However, they do not induce the production of new *neutrophils* in the *bone marrow* and they may decrease the number of other types of white cells, thus increasing the risk of infection. In general, steroids have not proven useful for patients with SCN, except for very few SCN patients not responding to other therapies, in whom steroids may be beneficial. In addition to the unwanted side effects of increasing the risk of infection, long-term use of steroids has many other side effects, e.g. it may induce the development of diabetes mellitus.

### **White cell transfusions**

*White blood cell* transfusions are rarely used. They are generally reserved for severe life threatening infections. The replacement of *neutrophils* by transfusion is not feasible in the long term for

various reasons. The collection of these cells is quite difficult, the mature neutrophil has quite a short life span and storage of the cells for more than a few hours only is impossible. As with all blood product transfusions, there is also a potential problem of viral infection with the transfusion.

## Supportive Treatment

There are a variety of supportive therapies; only the most important are addressed below:

- Mouth care - this should include regular dental check ups. Excellent oral hygiene is very important and the use of an antibacterial mouthwash is recommended.
- Immunisations and vaccinations - people with SCN have an intact immune system that allows them to make normal *antibodies* protecting from the devastating effects of viral illnesses. Therefore all routine immunisations according to the standard vaccination schedule of your country are recommended.
- Monitoring temperature - if you have a fever above 38.5°C/101.3°F you must seek medical attention.
- Good general hygiene including thorough hand washing.
- Oral *prophylaxis* – antibiotics/antifungals, either oral or intravenous, may be given to SCN patients but this is very much based on individual physician choice.
- Prompt contact of hospital/clinic - it is important to have the contact telephone numbers of your physician and clinic.
- Foreign travel - should be raised with your physician, as special precautions, emergencies and contact telephone numbers need discussion. A list of the neutropenia experts in different European countries cooperating with the SCNIR is given on page 31*f*.

## **LONG TERM MANAGEMENT OF SEVERE CHRONIC NEUTROPENIA**

The key issue in the treatment of SCN is the promotion of a 'normal life' for you. This includes schooling, vacations, family life and social life.

A *CBC/FBC* evaluation gives the physician the information needed to monitor your *ANC*. Monitoring the *ANC* alerts the physician to the need to adjust the *G-CSF* dosing.

When *G-CSF* treatment is initiated, your doctor will follow your *ANC* closely, generally for the first 4 to 10 weeks to check that the dose of *G-CSF* is correct for you. The Registry suggests that when the dose has been stabilised the SCN patient be monitored with monthly *CBC/FBC*. Blood should be drawn approximately 18 hours after dosing for patients on a daily administration of *G-CSF*. Patients taking *G-CSF* on a less frequent program should have the *CBC/FBC* done just prior to the next administration of the medication. This allows the physician to monitor the *ANC* at its lowest point prior to the next dose of *G-CSF*.

### **BONE MARROW MONITORING**

*Bone marrow* aspirate and biopsy procedures are done to help the physician diagnose the patient's medical condition. The *bone marrow* evaluation will help confirm if the patient has congenital neutropenia. After the diagnosis is confirmed, the Registry suggests that patients with congenital neutropenia be followed on a yearly basis with *bone marrow* and *cytogenetic* evaluations to monitor for changes in their *bone marrow*. SCN patients with types

of neutropenia other than congenital should have annual *bone marrow* testing at the discretion of their physician.

## **PREGNANCY**

The SCNIR collects information on SCN patients and pregnancy; however, the number of pregnancies reported to date is relatively small and thus little information is known about the potential effects of *G-CSF* during pregnancy. Therefore, the use of *G-CSF* during pregnancy should be evaluated individually with your primary physician, who can weigh the currently known risks and benefits of treatment in the context of your individual situation. Because the safety of *G-CSF* administration during pregnancy is not yet established, the current recommendation given by the experts of the SCNIR is that if possible, *G-CSF* should be avoided or minimized during the first trimester. You should discuss this issue with your physician well in advance of any decisions regarding pregnancy. It will then be possible for your physician to review the current pregnancy data with you and develop a plan for *G-CSF* dosing.

## **PSYCHOSOCIAL EFFECTS**

Family dynamics, school and employment can all be affected by the increased stress caused by the chronic illness of a family member. Families and patients with SCN may experience similar stresses to those found in families with a family member with diabetes, epilepsy, cystic fibrosis, or other long-term conditions. Children with SCN will experience the normal milestones of childhood along with the added stress caused by having a chronic condition.

After the diagnosis of SCN the patient and family may experience the common feelings of confusion, bewilderment, and possibly anger. SCN is difficult to diagnose. Some patients will have life threatening infections, others constant infections, while some experience only intermittent infections. There may be disruptions to normal family life because the untreated SCN patient may have unpredictable illnesses. Vacations or travel may be avoided or delayed because of the unpredictable nature of infections that may occur. Families may feel isolated from friends and community, needing to speak with other families that are dealing with this rare problem. Joining support groups, family or professionally led, will help with these feelings.

All pre-school children's developmental milestones include the mastery of their environment. Children with SCN need to be involved in their health care as is appropriate for their age. This may include learning to clean cuts and scrapes, proper hand washing, and helping with the administration of the *G-CSF*. At this age it may be beneficial for a child to be given a doll to care for that also is 'neutropenic' allowing the child to act as the doll's caregiver. The treated SCN child may want to act out giving the doll medication. This allows the child to act out the frustrations he / she is feeling regarding the neutropenia and to begin the process of learning necessary coping mechanisms.

All school-aged children utilise school for socialisation and academic development. This development is essential to help the child move through the milestones of childhood. The SCN child will need all caregivers (such as schoolteachers, school nurses, day-care providers, coaches) to understand SCN.

Adolescence is a difficult time for most children. Children with SCN will realise, often for the first time that they are different from

their peers. This may be the first time the child understands that he / she will have SCN for the rest of their life. The adolescent may feel that SCN affects school or relationships with peers. It is not uncommon for the adolescent to respond with denial of their condition. They may develop behaviours such as not caring for skin infections, lack of good oral hygiene or stopping the administration of the *G-CSF*.

At this stage the adolescent is struggling to maintain a positive self-image. The child may struggle against anything that appears to label them negatively. It is important for the parent to be alert to signs of change in habits or patterns that might indicate signs of depression or unusual anger (such as decreased interest in school or extreme behaviour). Parents need to trust their intuition and knowledge of the child's normal behaviour. If a parent becomes alerted or worried about changes in the adolescent's behaviour they should contact the primary health care provider to discuss their concerns.

## **THE SEVERE CHRONIC NEUTROPENIA INTERNATIONAL REGISTRY**

The Severe Chronic Neutropenia International Registry (SCNIR) was established in 1994 to monitor the clinical course, treatment, and disease outcomes in patients with severe chronic neutropenia (SCN). The Registry has the largest collection of long-term data on patients with this condition in the world. Participation in the Registry benefits patients, their families and the physicians who treat them by providing the most up to date information to them on the natural history of SCN and its treatment options.

**Severe Chronic Neutropenia International Registry**

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Patients qualify for the Registry if:

1. *ANC*'s are under 500 per mm<sup>3</sup> (0.5 X 10<sup>9</sup>/L) on at least three occasions in the three months prior to applying for the Registry (if currently treated, 3 *ANC*'s under 500 prior to the start of *G-CSF* therapy) with the exception of patients with Shwachman-Diamond *syndrome* who are enrolled with higher *ANC*'s or even no neutropenia at all.
2. There is a history of recurrent infections.

Patients do not qualify for the Registry if:

1. Their neutropenia is known to be drug-induced.
2. The patient has any one of the following conditions:  
*Thrombocytopenia* (SDS and GSD1b patients are an exception to this exclusion)  
*Myelodysplastic syndrome*  
*Aplastic anaemia*  
*HIV* positive  
Known immune diseases such as *rheumatoid arthritis*
3. The patient has had previous (within the past 5 years) *chemotherapy* for cancer.

For patients qualifying for the Registry the following basic examinations are required:

1. A *bone marrow* evaluation has been completed that confirms the diagnosis of SCN.
2. A *cytogenetic* evaluation has been completed, if *G-CSF* treatment has been considered or initiated.
3. The patient has signed a formal consent to allow the use of his/her anonymised data.

The objectives of the SCNIR are:

- Document the clinical course of SCN and monitor clinically significant changes e.g. primary treatment response over time and long-term safety.
- Study the *incidence* and/or outcome of the following previously identified adverse events: *osteoporosis, splenomegaly, vasculitis, thrombocytopenia, cytogenetic abnormalities, myelodysplastic syndrome, and leukaemia.*
- Establish a physician network to increase the understanding of SCN.
- Establish a demographic database to allow for future research.
- Collect *bone marrow* samples of patients at different time points for future research.

The SCNIR consists of:

An Advisory Board of expert physicians/haematologists:

- Dr. Mary Ann Bonilla, St. Barnabus Medical Center, West Orange, NJ, USA
- Dr. Laurence Boxer, University of Michigan, Ann Arbor, MI, USA
- Dr. Bonnie Cham, Manitoba Cancer Treatment & Research Foundation, Winnipeg, MB, Canada
- Dr. David C. Dale, SCNIR Co-Director, University of Washington, Seattle, WA, USA

- Dr. Melvin Freedman, Hospital for Sick Children, Toronto, ON, Canada
- Dr. George Kannourakis, Marian House, Ballarat, Victoria, Australia
- Dr. Sally Kinsey, St James's University Hospital, Leeds, West Yorkshire, UK
- Dr. Bertrand Liang, Amgen, Inc., Thousand Oaks, CA, USA
- Prof. Pier Giorgio Mori, Istituto Giannina Gaslini, Genoa, Italy
- Prof. Karl Welte, SCNIR Co-Director, Medizinische Hochschule, Hannover, Germany

And a panel of European physicians/haematologists called the Local Liaison Physicians located throughout the European countries:

- Dr. Tore Abrahamsen, Dept. Of Paediatrics, Rikshospitalet, Oslo, Norway
- Dr. Yigal Barak, Kaplan Hospital, Rehovot, Israel
- Dr. Marie Bruin, Het Wilhelmina Kinderziekenhuis, Utrecht, The Netherlands
- Dr. Göran Elinder, Södersjukhuset, Barnmedicinska kliniken, Stockholm, Sweden
- Dr. Evaristo F. Feliu, Hospital Germans Trias i Pujol, Badalona, Spain
- Prof. Andries Louwagie, A.Z. Sint Jan, Belgium
- Dr. Gundula Notheis, Dr. von Haunersche Spital klinik, Munich, Germany
- Dr. Juan J. Ortega, Hospital Materno-Infantil Vall d'Hebron, Barcelona, Spain
- Dr. Gert J. Ossenkoppele, Hospital Vrije Universiteit, Amsterdam, NL

- Prof. Jan Palmblad, Huddinge University Hospital, Huddinge, Sweden
- Dr. Helen Papadaki, University Hospital, Heraklion, Crete, Greece
- Dr. A.Y.N. Schouten-van Meeteren, Hospital Vrije Universiteit, Amsterdam, NL
- Dr. Sonja Shukry-Schulz, St. Anna Kinderspital, Vienna, Austria
- Dr. Owen Smith, Tallaght Hospital, Dublin, Ireland
- Dr. Geir Tjonnfjord, Rikshospitalet, Oslo, Norway
- Prof. Christiane Vermeylen, U.C.L. St. Luc, Brussels, Belgium

Information concerning the SCNIR can be obtained from:

### **In the USA**

Severe Chronic Neutropenia International Registry  
 Puget Sound Plaza  
 1325 4<sup>th</sup> Ave., Suite 620  
 Seattle, WA 98101  
 Phone +1(206)543-9749\*or (800)726-4463 (inside the U.S.)  
 FAX +1(206)543-3668\*

### **In Europe**

Severe Chronic Neutropenia International Registry  
 Medizinische Hochschule Hannover  
 Kinderklinik  
 D-30623 Hannover, Germany  
 Phone +49 (511) 557105\*  
 FAX +49 (511) 557106\*

## **In the UK**

Severe Chronic Neutropenia UK Registry  
Department of Paediatric Haematology & Oncology  
St James's University Hospital  
Leeds  
LS9 7TF  
Phone +44 (113) 206-5939\*  
FAX +44 (113) 247-0248\*

## **In Australia**

Cancer Research Centre  
University of Ballarat  
St. John of God Hospital  
1002 Mair St  
Ballarat  
Victoria  
Australia 3350  
Phone +61 (353) 33-4811\*  
FAX +61 (353) 33-4813\*

\*The + preceding the country code represents the local predial code for international calls.

## **WEB SITES**

**Severe Chronic Neutropenia International Registry**

Understanding Severe Chronic Neutropenia

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**In the United States:**

<http://depts.washington.edu/registry/>

**In Germany:**

[http://www.mh-hannover.de/kliniken/paed\\_haemonko/scn/](http://www.mh-hannover.de/kliniken/paed_haemonko/scn/)

## **SUPPORT GROUPS**

Support groups can provide assistance with linking families to others who have a family member with SCN. These contacts can help alleviate the alienation families often feel when one of their members is chronically ill.

### **Canada**

Neutropenia Support Association Inc.  
Phone (800) 663-8876 (inside Canada only)

### **Europe**

Interessengemeinschaft Neutropenie Hannover  
Phone +49 (4441) 911133\*

\*The + preceding the country code represents the local predial code for international calls.

### **USA**

National Neutropenia Network, Inc.  
Phone (800) 638-8768 (inside the U.S. only)

*Shwachman Syndrome* Support  
Phone (877) 737-4685 (inside the U.S. only)

## FREQUENTLY ASKED QUESTIONS AND ANSWERS ON SEVERE CHRONIC NEUTROPENIA

### **Q: Why does my child have SCN?**

Nobody truly knows how and why SCN develops. It is thought to be a disease that is genetically inherited. In patients with congenital neutropenia (*Kostmann syndrome*), it is thought to be inherited as an *autosomal recessive* disorder. This means that the affected patient's parents were carriers of the gene responsible for the disorder, and both passed that gene to their child. The only way your child can pass the disorder on to his/her children is if he/she married somebody else with a carrier gene.

Cyclical neutropenia is inherited as an *autosomal dominant* disorder. This is where one parent actually suffered to some extent from the condition himself or herself due to a gene that was 'dominant' over its partner gene. With cyclical neutropenia, there is a possibility that your child will pass the disorder onto his/her family.

However, in all subtypes of inherited neutropenia exceptions to the above mentioned pathway are possible, e.g. that in some cases the disease can occur for the first time in a family without having a parent carrying the gene.

### **Q: Will my child with chronic neutropenia develop normally, especially in their growth and development?**

Children with chronic neutropenias develop in the usual way. However, children with congenital neutropenia tend to be smaller



than individuals with other chronic neutropenias or those without neutropenia.

**Q: My child is due some vaccinations, is it safe for her/him to have them?**

In general, it is safe for your child to have vaccinations and all routine vaccinations are recommended to be given at the standard time intervals. Your physician will discuss any limitations based on your child's diagnosis.

**Q: My child recently had an extremely bad case of flu, which my doctor did not treat with antibiotics however, when my son cut himself after falling over the doctor did treat him with antibiotics. My doctor told me the difference was that flu was a different type of infection in which antibiotics would not be successful. I am now extremely confused as to what type of infections I should be looking out for. Can you please explain?**

*Neutrophils* are the most important cells against bacterial and fungal infections. Your child has a reduced number of *neutrophils* and hence is at greater risk of developing bacterial infections. Skin cuts, abrasions, ulcers etc. are at risk of becoming infected by bacteria. Bacterial infections are treatable by antibiotic therapy. In contrast, viruses cause most colds, flu and other childhood illnesses such as chickenpox. Antibiotics cannot treat these diseases, but normally the viruses are eliminated by *lymphocytes*, which usually are not reduced in your child's blood.

If you have any doubt about the type of infection your child has, you should take him to his physician.

**Q: What is the life expectancy of a child with chronic neutropenia?**

Before the availability of *G-CSF*, people with chronic neutropenia had many problems with infection. In some individuals, these infections were life threatening and some died from infection at a young age. Patients who are treated with *G-CSF* and have a near normal *ANC* should be able to have a normal life expectancy.

**Q: When should my child commence *G-CSF*?**

Your child should start *G-CSF* therapy if he/she is suffering from frequent mouth ulcers or infections that limit quality of life. People differ: the same neutrophil count in different individuals may result in different numbers of infections. The important thing is to reduce the number and seriousness of infections in your child whatever the baseline neutrophil count is.

**Q: Is there a safe limit to the amount of time you can take *G-CSF*?**

The SCNIR has information on many individuals who have received long term *G-CSF* treatment for more than eleven years. It indicates that long term *G-CSF* therapy is safe and remains effective.

**Q: Can you take *G-CSF* orally?**

*G-CSF* cannot be taken orally because it is a protein that would be destroyed by the stomach and intestines during the digestive process.

**Q: Is it safe to have surgery whilst on *G-CSF*?**

Yes - It is OK to have surgery as long as the surgeon is made fully aware of your condition and *G-CSF* treatment. You should obtain medical clearance from your haematologist prior to elective surgery and receive advice regarding your *G-CSF* dosing and schedule.

**Q: My daughter, who is aged 7, wants to attend a camp with her school. As she has severe congenital neutropenia and is receiving daily *G-CSF* that I administer to her, I am reluctant for her to attend but I also do not want her to miss out on these opportunities. Have you any advice?**

Your daughter should be encouraged to participate in all activities with children of her own age. Going away to camp will need special arrangements for storage and administration of *G-CSF* that can be arranged with the camp doctor/nurse. Alternatively, many paediatric haematology/oncology centres have summer camps in which physicians or nursing staff is able to administer medications.

**Q: My son has been receiving *G-CSF* since he was diagnosed with *Kostmann syndrome* three months ago. While he is a lot better he still tends to get breakthrough mouth ulcers, which cause him a lot of discomfort. Is there anything we can do to help alleviate his suffering?**

Children may benefit from good mouth care including flossing and regular dental check ups. Ensure that he has excellent oral hygiene, using mouthwashes such as chlorhexidine and difflam. It also may be useful to see your physician to discuss the dose of *G-CSF*; it may be that the dose needs modifying which could mean an increase.

**Q: I am 27 years old and have cyclical neutropenia. For this, I receive *G-CSF* three times a week. My boyfriend and I are getting married in a few months and soon after we would like to start trying for a family. Can you give me any advice on a) the chances of our child having cyclical neutropenia and b), any special precautions I should take whilst pregnant?**

The chance of your child also having cyclical neutropenia is 50% as long as your partner does not have cyclical neutropenia as well. This is because cyclical neutropenia is inherited in an *autosomal dominant* pathway. It would therefore be advisable to see a human geneticist to discuss your individual risk.

As *G-CSF* can cross the placenta to the foetus, it is best to discuss with your physician before you are pregnant *G-CSF* dosing options and develop a plan to deal with infections that may occur. At this present time we do not usually recommend the use of *G-CSF* in the first trimester if possible. If you are currently pregnant you should discuss what the dosing should be and what conditions caused by neutropenia would require you to contact your physician (such as fever or an infection).

**Q: Will a certain diet improve my disease?**

A good balanced diet will be beneficial for your family's overall health, as it will provide essential nutrients and vitamins to ensure good health and promotion of normal growth and development. There are no known vitamins, herb supplements or special diets that help raise the neutrophil level.

**Q: Can my child participate in school activities?**

Yes, providing that your child does not have a significantly enlarged spleen, low *platelets* or other medical condition he/she should be able to participate in all sports and other activities in the usual way. The school should be aware of your child's neutropenia and report any injuries to the parent.

**Q: What advice should I give to teachers at my child's school?**

Explain about your child's diagnosis and ask them to be vigilant for any fever or infections your child may develop. Ensure that they are aware though, that your child is able to fully participate in all school activities and should not be treated differently from any other child. (See addendum A)

**Q: Where and how can I get in contact with other patients?**

The SCN web page provides links to neutropenia-patient support groups in the USA and Canada. Your physician may be able to help you by looking at the SCNIR web page or, contacting the appropriate office in Australia, Germany, UK or USA (see page 32f). There are also many other non-specific patient support groups available to patients with SCN.

**Q: Where can I find more literature on the disease?**

The SCNIR web page has a reference list; in addition you can obtain literature by contacting the offices of the Registry (see page 32f).

# ADDENDUM A

## Information for Schools regarding Severe Chronic Neutropenia

To: \_\_\_\_\_

From: \_\_\_\_\_

Severe chronic neutropenia (SCN) is the name given to a group of conditions in which neutropenia is the primary problem. The term neutropenia describes the situation where the numbers of *neutrophils* in the blood is too low. The *neutrophils* are very important in defending the body against bacterial infections and therefore, a patient with too few *neutrophils* is more susceptible to bacterial infections. This condition is not contagious and cannot be spread from one person to another. It is genetic blood disorder. Specific neutropenias are passed from the parent's DNA to the child's DNA, the same way the child would acquire red hair or blue eyes.

Neutropenia is treated with injections of a cytokine called *G-CSF* or Neupogen. This helps the body create *neutrophils* to fight infection.

Please help us to fight infections by cleaning minor cuts and with an antibacterial soap or betadine. Please notify me the day of the injury so that I may continue to monitor the wound. For wounds that may need special care please notify me immediately.

For fever above \_\_\_\_\_ please call me immediately.

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If you have concerns about my child's health you may reach me at the following telephone numbers:

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For more information regarding neutropenia please contact the SCN Registry, or me. The web address is:

<http://depts.washington.edu/~registry/>

## GLOSSARY

**ANC (absolute neutrophil count)**, determined by adding the percentage of *neutrophils* in the blood with the percentage of *bands* in the blood, multiplying that number by the *white blood count* and dividing the product by 100. This number represents the amount of *neutrophils*, which are available for defending the body at the time of the blood test. A normal *ANC* for a non-neutropenic person is generally within the range of 1800-7000.

**Acute myeloid leukaemia (AML)**, an acute form of *leukaemia*, a malignant disease of the *white blood cells* affecting *monocytes* or *granulocytes*. It is characterised by the appearance of immature, abnormal cells in the *bone marrow* and peripheral blood.

**Alopecia**, loss of hair.

**Anaemia**, too few red blood cells.

**Antibodies**, proteins made by a subgroup of *white blood cells*, the *lymphocytes* that are responsible for the body's defence. *Antibodies* are normally directed against foreign structures like pathogens or transfused cells. However, sometimes they may also be directed against structures and cells of their own body, e.g. in the case of anti-neutrophil *antibodies* where the *antibodies* recognise and destroy the patient's own *neutrophils*.

**Aplastic anaemia**, a deficiency of all of the formed elements of the blood, representing a failure of the cell generating capacity of the *bone marrow*.

**Arthralgia**, painful joints.

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**Arthritis**, inflammation of joints.

**Autosomal dominant**, a particular type of genetic inheritance. In a dominant inheritance pathway, like in cyclic neutropenia, the child will become a cyclic neutropenia patient if either one of her/his parents pass the affected gene on to their child. The addition '*autosomal*' refers to the fact that the inheritance is independent of the child's sex.

**Autosomal recessive**, a particular type of genetic inheritance. In a recessive inheritance pathway, like in Kostmann *syndrome*, the child will become a Kostmann patient only if both parents pass the affected gene on to their child. The addition '*autosomal*' refers to the fact that the inheritance is independent of the child's sex.

**Bands**, juvenile *neutrophils*. These are usually counted as *neutrophils* and contribute to the *absolute neutrophil count*.

**Basophils**, a subgroup of *granulocytes*, which may increase after *splenectomy*.

**Bone marrow**, the spongy material located in the centre of our bones. It is the home of our *stem cells*, which reproduce to create our blood, including *white blood cells*, red blood cells, *platelets*, B- and T *lymphocytes* and macrophages.

**CBC (Complete Blood Count)**, a summary of the numbers of various types of cells present in the blood at the time of the blood draws, same as *FBC*.

**Chemotherapy**, a drug treatment to destroy cancer cells.

**Chromosomes**, carry all genetic information and are located in the cell nuclei. Changes of the *chromosomes* may indicate the development of a disease. They may be detected by certain examinations like *cytogenetics*.

**Cutaneous**, concerning the skin.

**Cytogenetic**, concerning the *chromosomes*.

**Cytogenetics**, a method by which *chromosomes* can be analysed under the microscope.

**Differential blood count**, the subclassification of *white blood cells*.

**Erythrocytes**, red blood cells.

**FBC (Full Blood Count)**, tests, which show what amount of various types of cells, or substances are available in your blood, same as *CBC*.

**Filgrastim**, the international non-proprietary name for r-metHuG-CSF.

**G-CSF**, *granulocyte*-colony stimulating factor.

**G-CSF receptor**, a structure on the surface of *granulocytes* to which *G-CSF* binds. After binding to a receptor, the cell receives information on how to proceed, e.g. grow, divide, mature etc.

**Genetic engineering**, a method by which, for example, the human gene for *G-CSF* is transferred into cells from another species like bacteria, which in turn produce the desired product in large scale.

**Granulocyte**, a subtype of *leukocytes*, which can be further distinguished into *neutrophils*, eosinophils and *basophils*.

**Haematopoiesis**, the formation of blood

**Haematopoietic growth factor**, a protein stimulating the production (growth) of blood cells.

**Haematuria**, the occurrence of blood in the urine.

**Hepatomegaly**, the enlargement of the liver.

**HIV**, the human immunodeficiency virus.

**Incidence**, the number of new cases of a certain disease in a certain time period.

**Lenograstim**, the international non-proprietary name for glycosylated rHuG-CSF.

**Leukaemia**, a malignant disease of the *white blood cells*.

**Leukocytes**, *white blood cells* consisting of *granulocytes*, *monocytes* and *lymphocytes*.

**Lymphocytes**, subgroup of *leukocytes*, which are responsible for the body's defence against viruses (T *lymphocytes*) and the production of *antibodies* (B *lymphocytes*).

**Metabolic**, refers to the balance between uptake, degradation and utilisation of food.

**Monocytes**, a subgroup of *leukocytes*, which eliminate infectious particles and infected cells by eating and digesting them.

**Morphological**, refers to the physical shape and size.

**Myelodysplastic syndrome (MDS)**, a *syndrome* characterised by the appearance of atypical cells in the *bone marrow*. *MDS* can progress to *leukaemia*.

**Myelokathexis**, a very rare form of *congenital* neutropenia that is characterised by the inability of the *neutrophils* to leave the *bone marrow* and enter the blood.

**Neutrophils**, a subgroup of *granulocytes* defending the body against bacteria. *Neutrophils* are also known as segs, polys or segmented *neutrophils*.

**Osteopenia**, mildly demineralised bone substance.

**Osteoporosis**, severely demineralised bone substance.

**Platelets**, a subgroup of blood cells responsible for clotting, which are also called *thrombocytes*.

**Pluripotent haematopoietic stem cell**, cells that still have the potential to develop into any blood cell.

**Promyelocytes**, precursors of *granulocytes* in the *bone marrow*.

**Prophylaxis**, any procedure to avoid undesired events e.g. the development of infections.

**Proteinuria**, the occurrence of protein in the urine.

**Psoriasis**, a disease characterised by scaly skin.

**Rheumatoid arthritis**, chronic inflammation of several joints also referred to as polyarthritis.

**Splenectomy**, surgical removal of the spleen.

**Splenomegaly**, the enlargement of the spleen.

**Stem cells**, the most immature cell in the *bone marrow*, which are able to reproduce themselves and develop into different types of blood cells.

**Subcutaneous**, under the skin.

**Syndrome**, a complex of various disease symptoms.

**Thrombocytes**, a subgroup of blood cells responsible for clotting which are also referred to as *platelets*.

**Thrombocytopenia**, the decreased number of *platelets* in the blood ( $< 150\,000$  per  $\text{mm}^3$ ).

**Vasculitis**, the inflammation of small blood vessels.

**White blood count**, the total number of *leukocytes* in the blood at the time of the blood test.

**White blood cells**, a subgroup of blood cells consisting of *monocytes*, *granulocytes* and *lymphocytes*, which together build the immune system and defend the body against infection.