WANT TO LEARN MORE?

If you would like more information on anything you have read in this newsletter, or on any aspect of the Waldenström Macroglobulinemia Family Study, please contact:

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Information about the NCI Genetic Epidemiology Branch may be found on the Web at http://dceg.cancer.gov/geb

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Cancer Institute

Division of Cancer Epidemiology and Genetics (DCEG)

The Power of Families

Waldenström Macroglobulinemia Family Study Newsletter

Spring 2010

Thank you for taking part in the Waldenström Macroglobulinemia (WM) Family Study. Our research team is truly grateful to you and your family members for taking part in this study. We appreciate the time and energy you gave to completing the questionnaires, giving us access to your medical records, and providing samples for our research. We hope that you will continue to assist us in this effort.

So far, 116 families are taking part in this study, totaling 567 people. These include men and women with WM, their close family members, spouses and other relatives. Most participate from their home communities by filling out questionnaires and giving samples.

We would like to update you about our study activities and the scientific findings that you make possible. We hope that you will find the articles that follow informative.

If there are any topics or questions that you would like to see in future newsletters, or if you have questions about the information discussed in this newsletter or anything related to the study, please let us know. We welcome your phone calls, letters, or e-mails.

Each of you has made a vital contribution to this research. Our research simply would not be possible without your willingness to take part in this study. Please accept our heartfelt "thank you" for all you have contributed to advancing our understanding of familial Waldenström macroglobulinemia.

Mary L. McMaster, MD
Lead Investigator

The Problem of 'Medicalese' in WM

Wading through 'Doctor Talk'

WM is a complex disease. Researchers and healthcare professionals have developed a complex language to describe it. We have found that our patients and their families usually know a lot about WM. However, it can often be hard to understand the language we use. We created a **Glossary** to explain some of the terms that may be unfamiliar to you. Words or phrases that are underlined appear in the Glossary starting on page 15. Let us know if you have suggestions for other terms to include in this list. The **Resources and Links** section lists excellent resources for patients and their family members who are trying to "learn the lingo."

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How You Can Help The Study

We are very interested in news about you and your family. If your family has had changes in address, births, new illnesses diagnosed or family members who have passed away, please let us know. Please complete and send back the enclosed "Family Update Form," or contact our research nurse by phone or email. Each piece of information we receive from you brings us a little closer to understanding the mysteries of WM. We hope you will continue to help us by reporting your latest information and donating more blood, if needed. Our research cannot go forward without the help of families like yours.

You may reach the Study Team directly by using our contact information found at the bottom of page 1 and on the back cover of this newsletter.

We are very interested in news about you and your family.

Study Findings — What Are We Learning About Familial WM?

Features of Familial WM

From studying 40 years of WM patient records, we have found that patients with familial WM are often diagnosed at a younger age than patients with sporadic WM. Many familial cancer syndromes share this feature. Young age at diagnosis suggests that a person's genes may contribute to WM susceptibility. In some families, a parent and their child(ren) had WM. In other families, only brothers and/or sisters had the disease. These patterns are important because they provide us with clues about whether and how susceptibility to WM is inherited.

In some families, relatives without WM had mild changes related to their immune system. These were usually minor changes in laboratory tests and caused no illness. Occasionally, the relatives had symptoms from an immune disorder.

Some relatives also had high or low levels of immunoglobulin (a protein that helps the body's immune system), including a condition known as monoclonal gammopathy.

We do not know whether these immune differences are more common in relatives of familial WM patients compared to the general population. They were not present in every family. When they occurred in a particular family, they were not present in every member of that family. We need to do more research to understand these findings.

We would like to build upon the information we have about WM patients with and without a family history of the disease. We need to know about how WM behaves in all families, not in just some of them.

Patterns are important because they provide us with clues

Why is it Important to Know My Family's Medical History?

A family medical history is a record of health information about a person and his or her close relatives. A complete record begins with information from three generations of relatives, if available. Three generations of relatives include children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and first cousins.

Many factors influence the development of complex disorders such as cancer. Families often share many of these factors. These factors may be genetic, environmental or lifestyle-related. Together, they can give clues to medical conditions that may run in a family. By reviewing family history, healthcare professionals may notice patterns of disorders among relatives. They can then determine whether an individual, other family members, or future generations may have a higher-than-usual chance of developing a particular condition.

If you have relatives with a medical condition, this does not mean that you will definitely develop that condition. A person with no family history of a disorder may still be at risk of developing that disorder. Knowing one's family medical history may allow a person to take steps to lower his or her risk.

The easiest way to get information about family medical history is to talk with your relatives about their health. Have they had any medical problems; if so, when did they occur? Getting copies of medical records and other documents (such as obituaries and death certificates) can help complete a family medical history. It is important to keep this information up-to-date and to share it with your healthcare professional regularly.

There are many ways to record information about family history. The Department of Health and Human Services provides a private, internet-based tool to help individuals record and draw their medical family tree (called a pedigree). This tool, along with information about how to use it, may be found at https://familyhistory.hhs.gov.

Searching for WM Genes

Cytogenetics

Cytogenetics is the study of our chromosomes. Chromosomes are the 23 pairs of threadlike 'packages' that hold all of our genes. Genes are made up of DNA. We can see chromosomes by looking at cells under a microscope. We sometimes see a break in a chromosome. This usually means that a particular piece of DNA has been damaged. Sometimes, these breaks can cause a cancer to develop. Cancer can also develop without a visible break. Since cancer cells are unstable, their chromosomes are more likely to break than the chromosomes in normal cells. In other words, sometimes a damaged chromosome can cause a cancer, and sometimes a cancer can cause damage to chromosomes. One of our challenges as researchers is figuring out which came first.

We know that many blood cancers (leukemia) and lymph node cancers (lymphoma) involve breaks in chromosomes. In certain leukemias, the chromosome breaks are so specific that they can be used to help diagnose the leukemia. Researchers have found some chromosome changes in WM cells. But these changes are not specific for WM. Researchers have not yet found a unique chromosome change that is present in WM cells in all patients.

Researchers recently discovered that many – but not all – WM patients have damage to a particular chromosome. The damage causes loss (or deletion) of a piece of chromosome 6. This finding led scientists to ask whether damage to chromosome 6 may be the first step leading to WM, including familial WM.

We used cytogenetics to study bone marrow cells from patients in our study. We found chromosome damage in the cells of some familial WM patients. Most of these damaged chromosomes also occur in patients who have sporadic WM. The damaged chromosomes were usually different in each patient. This was true even in patients who were from the same family. Our conclusions were:

- We did not find that deletions of chromosome 6 were more frequent in familial WM patients compared to patients with sporadic WM.
- The chromosome changes found in familial WM appear to be similar to those found in non-familial WM.
- Most importantly, **we found no evidence that these particular chromosomal changes are inherited.**

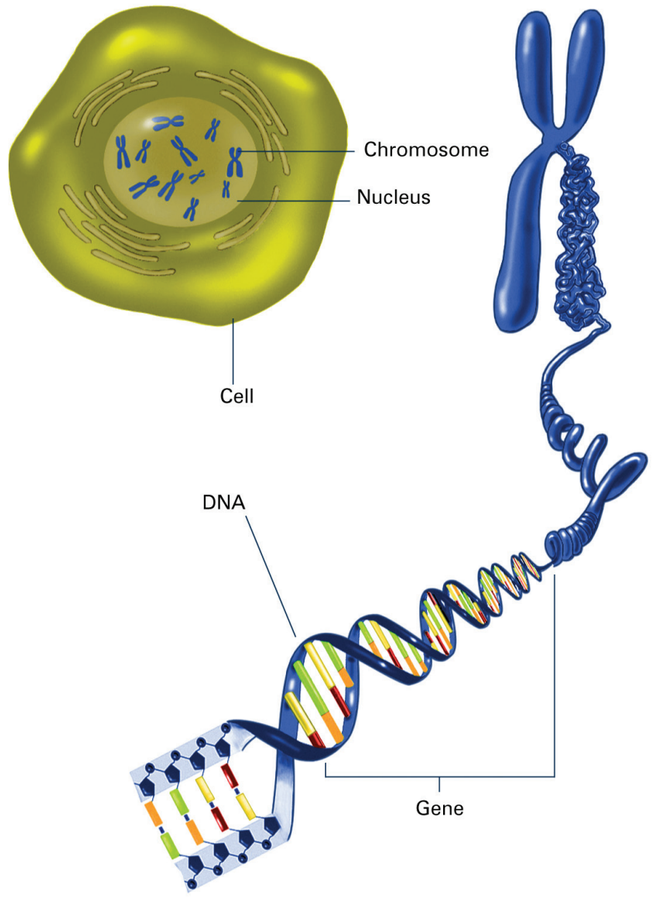
Based on this research, we are looking for other ways to find susceptibility genes for WM.

Linkage study

An important way of searching for genes that might be involved in WM is called linkage analysis. In linkage analysis, researchers use statistics to study family and laboratory information. We use this information to look for locations on chromosomes containing genes that may be related to WM. We can only do linkage analysis if we have DNA from many WM families, including family members who have WM and those who do not have the disease. This is one reason why every member of every family that participates in our research is so important.

Linkage analysis is complicated. Researchers use genetic markers in DNA to follow the patterns of genes as they are passed from generation to generation or shared among relatives. We look for a change in the expected pattern. For example, we may look at the genes of many pairs of relatives with WM. If they share more genetic markers in a particular region of a chromosome with each other than with their relatives who do not have WM, we say that WM is "linked" to that particular chromosome region.

We conducted a linkage study using information from some of our WM families. We discovered that many people with WM shared genetic markers in four chromosome regions. These are our first clues about where to look for WM-associated genes. In future studies, we will be looking at ways to narrow these regions down. We will also be looking for more families with WM, since we want to know whether these regions are important in most WM families or only a few.



A cell showing the packaging of DNA into chromosomes within the cell's nucleus. Genes occur along segments of a continuous strand, or molecule, of DNA. Altogether, genes carry the complete set of instructions for making all the proteins a cell will ever need. Separate strands of DNA are coiled into structures called chromosomes.

We now know that IgM MGUS can be a precursor condition for WM.

Candidate genes

The candidate gene approach searches for specific genes that might be related to the development of WM. Unlike a linkage study, in a candidate gene study we already have clues about which genes might be important. For example, we already know that some genes play a role in lymphoma or multiple myeloma, two conditions that are related to WM. We might expect that these genes play a role in WM as well. Another clue is finding chromosome breaks that occur within or very near specific genes that we know are important in bone marrow cells.

Once we have chosen a candidate gene to study, we use DNA samples to look for changes in that gene in family members who have WM and those that do not. As a practical issue, studying candidate genes takes a lot of time, uses precious DNA, and is very expensive, so we want to choose the candidates very carefully.

We recently studied a panel of candidate genes. The panel included genes that are involved in immune function, normal blood cell function, and inflammation. These genes have different forms (or alleles). We found a small group of genes that are more likely to appear in one form in WM patients and in a different form in their unaffected relatives. We do not believe that any of these genes, by themselves, cause WM. A change in any of these genes is likely to have a very small effect on risk for WM. However, they may act with other genes or environmental factors to influence susceptibility to WM. We are planning more studies to confirm our findings.

Precursor Conditions for WM

We know that some types of cancer have a precursor condition. A precursor condition is a collection of unusual cells that are more likely than normal cells to develop into cancer. In the past, the only blood cancer known to have a precursor condition was multiple myeloma. The precursor condition for multiple myeloma is called MGUS or monoclonal gammopathy of undetermined significance. The hallmark of MGUS is the presence of an excess amount of a specific protein called immunoglobulin. The most common immunoglobulins are IgM, IgG, and IgA. IgM MGUS is related to WM. The MGUS protein related to myeloma is usually IgG or IgA.

At the beginning of the WM family study, we noticed that some of our patients' healthy relatives had IgM MGUS but no sign of WM. When we looked very carefully, we could also find tiny amounts of IgM MGUS protein in other relatives and sometimes in healthy *unrelated* people. To learn more about this, we went back to data collected from our earliest participants and studied them in more detail. We found that if the amount of IgM MGUS was very small, it often disappeared over time. Among people who had a measurable amount of IgM MGUS, some *but not all* went on to develop WM after many years. We reported these findings at the Second International Waldenström Macroglobulinemia Workshop in 2002. Other scientists became interested in this topic and did more research of their own.

We now know that IgM MGUS can be a precursor condition for WM. It is important to understand that precursor conditions do not always lead to cancer. In fact, precursor cells usually disappear with time. Cancer develops *only* if the precursor cells go through more genetic changes. For now, we cannot predict whether a person with IgM MGUS will go on to develop WM. This is an area of concern to many of our families. We are planning to continue to study it in detail and will keep you informed.

Related Research News

We work with researchers around the world who are interested in WM and related blood and lymph node cancers. Below is a summary of some of the other research that we are doing to better understand WM.

Studies of WM and B-cell Cancers in the General Population

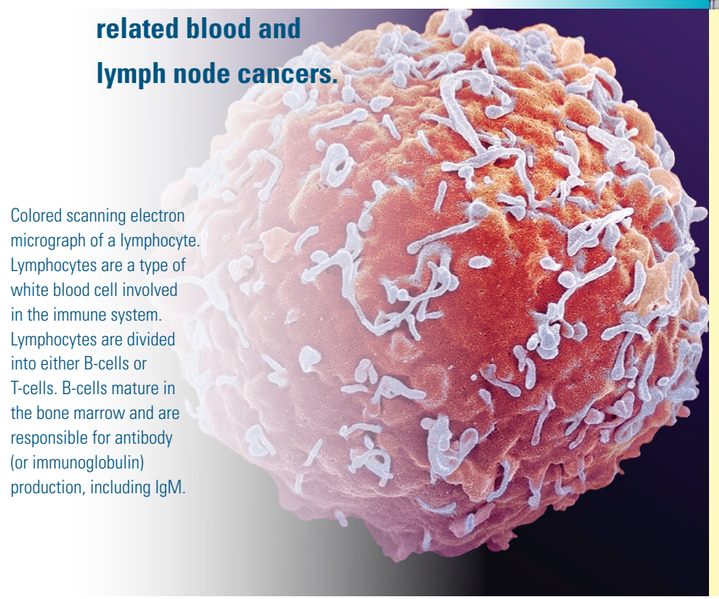
What is a B-cell?
Our blood contains many different types of cells. Each type of cell has a special job to keep us healthy. One special type of blood cell is the B-lymphocyte or B-cell. B-cells are important in immune function. A healthy immune system allows us to fight infections and to rid our bodies of diseased cells. B-cells pass through several stages as they mature. Most of the time, B-cells are on 'stand-by' in our blood, lymph nodes and bone marrow. However, when germs invade our bodies, B-cells are 'activated.' An activated B-cell begins making large amounts of antibodies (also called immunoglobulins) to fight the germs or diseased cells.

Is WM a type of B-cell cancer?
Yes. Although relatively rare, a cancer can arise from a B-cell at any stage of its development. WM affects B-cells that have almost completely matured. Other cancers that affect B-cells at different stages of their development include chronic lymphocytic leukemia (or CLL), multiple myeloma, Hodgkin lymphoma, and many types of non-Hodgkin lymphoma. These cancers are related, even though each has special features. Researchers are working to understand more about how these cancers are related.

Do relatives of WM patients have a higher-than usual chance of developing WM or a related B-cell cancer?
Yes, we have found that relatives of patients with WM had a higher-than-usual chance of developing WM as well as two other related B-cell cancers, called non-Hodgkin lymphoma and chronic lymphocytic leukemia.

WM and other B-cell cancers are rare.
Even though relatives have a higher-than-usual chance of developing them, the overall chance remains low. For example, CLL is about 20 times more common than WM. The lifetime chance for any person to develop CLL is less than 1 in 100. Although a close relative of a WM patient is about two times more likely to develop CLL than someone who is not related to a WM patient, the chance is still less than 1 in 100.

We work with researchers around the world who are interested in WM and related blood and lymph node cancers.



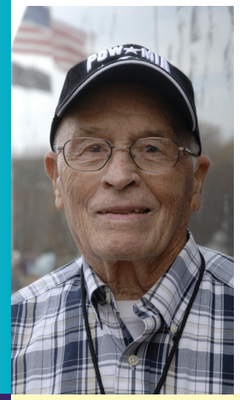
Colored scanning electron micrograph of a lymphocyte. Lymphocytes are a type of white blood cell involved in the immune system. Lymphocytes are divided into either B-cells or T-cells. B-cells mature in the bone marrow and are responsible for antibody (or immunoglobulin) production, including IgM.

Risk Factors for WM

WM is more likely to develop with age and is more common among men.

We knew from earlier population-based studies that the risk of developing WM is related to age and gender. WM is more likely to develop with increasing age and is more common among men.

Those same studies suggested that WM risk might also be related to race, because WM is more than twice as common in whites as in African-Americans. However, very little was known about other factors that may increase the chance for a person to develop WM. Our research has added to what we know about the potential risk factors for WM.



Influence of Race on Risk for WM
Studies done in the 1990s showed us that in the U.S.:

- African-Americans are only half as likely as whites to develop WM.
- But they are twice as likely as whites to develop multiple myeloma, a related cancer.

These differences could be due to genetic factors, or they could be due to differing environmental exposures.

If environmental exposures are important, then we might see differences between African-Americans and Africans. We tested immunoglobulins in over 900 African men in the country of Ghana. We then compared their results to those from white men in the U.S. We found that African blacks are nearly twice as likely as U.S. whites to have the precursor condition of multiple myeloma, called MGUS (**m**onoclonal **g**ammopathy of **u**ndetermined **s**ignificance). This is similar to the pattern for blacks and whites in the U.S. We then looked at the specific type of MGUS (IgM MGUS) that we have found to be a precursor condition for WM. (See **Precursor Conditions for WM** on page 5.) We found IgM MGUS in only 6% of African blacks, compared to 14% of U.S. whites. In other words, African blacks and African-Americans appear to have similar patterns of both MGUS overall and IgM MGUS compared to whites. **While this finding does not explain why blacks in the U.S. seem to be less likely than whites to develop WM, it does suggest that there may be factors related to race that influence susceptibility to WM.**

Chronic Immune Stimulation and Risk for WM

We studied over 4 million U.S. veterans who were hospitalized in VA hospitals during a 27-year period (1969 – 1996). We identified patients who were diagnosed with WM and compared them to veterans who were not diagnosed with WM. For both groups, we collected information about autoimmune diseases, allergic conditions, and a variety of infections. We found that patients who developed WM were more likely to have had a prior history of autoimmune disease or certain infections, but not allergies. **These findings do not mean that autoimmune diseases or infections cause WM. They do give us some ideas about important biological mechanisms that we hope to evaluate further.**

We studied over 4 million U.S. veterans who were hospitalized in VA hospitals during a 27-year period (1969 – 1996).

Future Research — Where Do We Go From Here?

Lessons from the Questionnaires

We are now analyzing the data that you provided in your questionnaires when you first enrolled in the study. We hope to use this information to learn more about the WM disease process when there is a family history of WM by finding answers to questions such as:

- If you have a family history of WM, are you likely to have the same kinds of symptoms as someone without a family history?
- Is your WM more or less likely to need treatment early?
- Are there any conditions or exposures that occur more often in family members with WM than in unaffected family members?

We hope to have answers to these questions soon.

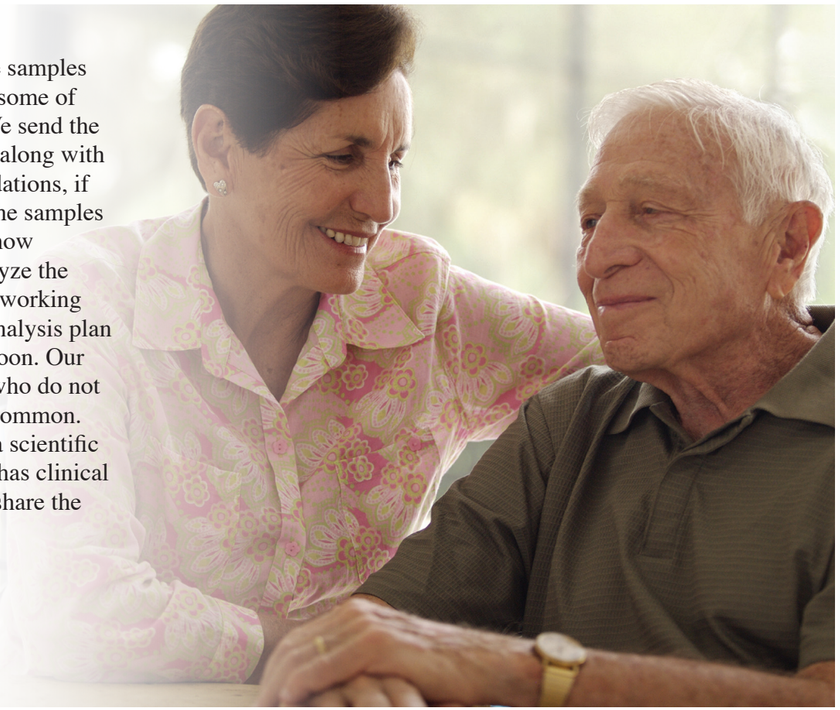
Lessons from Genetic Analyses

We were very excited by the results of our first linkage study (see **Linkage study** on page 4). We identified four regions of the genome that may contain WM susceptibility genes. Each region is very large and contains hundreds of genes. Studying every gene in these regions is not practical, so we want to confirm our results before we start a detailed analysis.

Fortunately, WM families are continuing to enroll in this study. We are planning a larger linkage study focusing on families that have more than two members with WM. By focusing on larger families, we will have greater confidence in our results. In addition, because there are more people with WM in these families, we expect that any WM genes will be more common and hopefully easier to find. We are also excited because this linkage study will be an international effort. One of our goals is to foster successful teamwork among scientists worldwide.

Lessons from Lab Tests

When you donate blood and urine samples for the WM family study, we use some of the samples for clinical testing. We send the results of that testing back to you along with our interpretation and recommendations, if applicable. We also use some of the samples for research laboratory tests. We now have enough data to begin to analyze the laboratory tests. We are currently working with statisticians to develop the analysis plan and expect to begin the analysis soon. Our goal is to see if family members who do not have WM have other features in common. We plan to publish our results in a scientific journal. If we learn anything that has clinical importance for you, we will also share the information with you directly.



How Do We Protect Your Rights and Confidentiality?

Patients sometimes ask us what procedures we have in place to protect their confidentiality. They may be concerned about their ability to obtain insurance in the future. Others may prefer to keep information about their diagnosis private, even within their family. Still others may wonder who has access to their samples and for what purpose.

Protecting your privacy is our utmost concern, so we want to share with you more details of how the NCI handles your information and samples:

- When we first design a study, we describe how we will protect our participants' privacy. We also make every effort to list the specific uses we intend for the samples and to give scientific reasons why lab studies are necessary. All of our study plans are reviewed by the NCI's Institutional Review Board (IRB). The IRB is made up of scientists, doctors, clergy, and consumers from both within and outside NCI. The IRB reviews the study procedures annually and has the right to stop the research if it believes the risk to the participants is too high, the participants' privacy is not adequately protected, or the scientific reasons are not sound.
- At the beginning of a study, each participant signs an informed consent form. This form describes the study and outlines possible uses of samples in the future. Those who take part in the study can allow or decline use of their samples for these purposes. If we find new uses for your samples beyond those listed in the study design or consent form, then we must bring new proposals to the IRB for review and approval.
- We collect samples and store them in a special laboratory to keep them in a stable condition. These are closely-guarded, highly-secure facilities. All samples are given a code number and do not carry your name or other identifying information. The only people who can make the connection between the code and your personal data are those NCI staff who are directly involved in this specific study.
- The study has a Certificate of Confidentiality, which protects researchers and/or institutions from being compelled to disclose any information that would identify study participants, thereby protecting the privacy of research participants. The researchers involved in this study have pledged to keep all information confidential. For more information on Certificates of Confidentiality, please visit http://grants2.nih.gov/grants/policy/coc/.
- Because the purpose of our research is to increase understanding of WM, it is important for us to share our research results with the scientific community. This is usually done by presenting our results at scientific meetings or preparing articles for publication in scientific journals. We will not identify you individually in any publication or presentation resulting from this study.

All samples are given a code number and do not carry your name or other identifying information.

Our study is part of the research program of the Genetic Epidemiology Branch (GEB) within the National Cancer Institute's (NCI) Division of Cancer Epidemiology and Genetics (for more information about who we are and the work we do, please visit http://dceg.cancer.gov/). NCI is part of the National Institutes of Health, the Federal Government's biomedical research agency.

Our goal is to learn as much as we can about familial WM as quickly as possible, without placing you or your privacy at risk.

Your samples are an incredibly valuable gift to science and the community at large. Thank you again for your remarkable generosity.

What is MGUS?

'MGUS' stands for 'monoclonal gammopathy of undetermined significance'. IgM is one type of special blood protein called an immunoglobulin, or antibody. Immunoglobulins are made by a type of specialized white blood cell called a 'B-lymphocyte' or 'B-cell'. All IgM molecules share similar features. However, the IgM made by a given B-cell will have very small differences from the IgM made by all other B-cells. Usually, IgM is constantly produced at a low level by many millions of B-cells. This normal IgM is called polyclonal ('poly' means 'many' and 'clonal' refers to cells). Sometimes, a B-cell makes identical copies of itself. Then, all these identical B-cells (called a 'clone') will make identical IgM molecules. When this happens, an excess of IgM develops. The condition of having excess identical IgM molecules is called 'monoclonal gammopathy' ('mono' means 'one' and 'gammopathy' refers to atypical immunoglobulins). If there is enough monoclonal protein, then we can identify and measure it using a laboratory test called protein electrophoresis. This is sometimes called the "M-spike" because of how it looks on the laboratory test result.

By itself, monoclonal gammopathy doesn't tell us much. Many conditions can cause B-cells to make excess immunoglobulin. For example, certain inflammatory conditions, infections, autoimmune disorders and drug reactions may be associated with a monoclonal gammopathy. Sometimes, a cause for the monoclonal gammopathy cannot be found. When we can find no cause for the monoclonal gammopathy, we say that it is of unknown or 'undetermined' significance. We then call it MGUS.

MGUS occurs in about 3% of healthy adults. It becomes more common as we age. MGUS is very rare under age 30 and is thought to occur in 10% or more of people at age 80. In most cases, MGUS disappears or stays the same over time. This is especially true when there is only a small amount of the MGUS protein. If the MGUS persists, a small number of individuals with it will develop a blood or lymph node cancer. Most people with MGUS never develop any serious disease. However, a small number of individuals with IgM MGUS may develop WM, chronic lymphocytic leukemia, or another non-Hodgkin lymphoma.

At What Age is WM Usually Diagnosed?

The "typical" WM patient is diagnosed at about age 70. If you read medical articles about WM, you will often see a younger average age quoted, usually 63 – 65 years. Remember that most medical articles come from universities that are reporting on the patients in their clinical trials. Older patients may be less likely to participate in clinical trials and so would not be included in these articles.

What Part(s) of the Body Does WM Usually Affect?

By definition, WM affects the bone marrow, although the WM cells may be hard to find early in the disease. The next most common areas are lymph nodes and spleen. WM tumor cells can sometimes be found in unusual locations, such as around the eye or in the intestinal tract, lungs or skin.

WM is unique among cancers in that symptoms can be caused by either the WM cells or the IgM protein. The IgM protein circulates in the blood. Since blood travels to every part of the body, then it is possible to have IgM-related symptoms anywhere. IgM can cause symptoms in two ways: 1) because of its size, and/or 2) because it is an antibody. Most IgM-related symptoms that are due to the size and/or "stickiness" of the IgM protein are part of the hyperviscosity syndrome. Because it is an antibody, IgM can cause symptoms by attacking body tissues by mistake. Peripheral nerves (that is, nerves outside the brain and spinal cord) and various blood cells are the most common targets of mistaken IgM attack. Patients with peripheral nerve involvement may experience numbness or a painful or burning sensation in their feet or hands. If blood cells are targeted, patients may develop a low red blood cell count, called anemia or a low platelet count, called thrombocytopenia.

Are Other Cancers Associated with WM?

There are two parts to this question. First, is a patient with WM more likely to be susceptible to other cancers? We do not yet know the answer to this question. Studies with a large number of patients are needed to further evaluate this question.

The second part of this question is whether the relatives of a WM patient are susceptible to WM or other cancers. We have some information about other blood and lymph node cancers in family members of WM patients. We recently found that, if a person is diagnosed with WM, then his/her close relatives (parents, siblings, and children) are at slightly increased risk for chronic lymphocytic leukemia and non-Hodgkin lymphoma. See **Research News** on page 6 in this issue for more information about this finding.

How Much do Environmental Factors Affect WM?

We do not yet know the answer to this question. We hope to get some clues from our analysis of your questionnaire information. Some recent studies (see **Research News**) have looked at infections prior to WM. They found that patients with WM were more likely to have had certain infections, such as hepatitis C and HIV, the virus that causes AIDS, than patients without WM. That does not mean that these infections cause WM. It is more likely that there is some common link between these infections and WM, such as problems with the immune system.

Can WM be Prevented?

Until we know what causes WM, we can only have an educated guess about what might help prevent it. Data suggest that immune function may be related to WM. WM can also cause problems with immune function, so it can be hard to tell which comes first. There are steps you can take to encourage a healthy immune system. These include:

- Choose healthy foods
- Get regular exercise
- Get plenty of sleep
- Practice stress-reduction strategies
- Avoid tobacco products
- Practice sun safety; avoid sunburns

Are There Foods that Increase Blood Counts?

Low blood cell counts in WM are usually caused by the WM cells 'crowding out' the normal blood-forming cells in the bone marrow. Also, the IgM can sometimes attack the blood cells and cause low blood counts. When low blood counts are due to these effects of WM, specific foods are not likely to increase the blood counts. Instead, the low blood counts are usually a very good reason to treat WM. Successful treatment of WM often allows the blood counts to recover.

Nutrition may influence certain types of blood counts. Low red blood cells (called anemia) may be due to iron deficiency or deficiency of other specific nutrients such as folate or vitamin B12. Consult your healthcare provider if you have anemia from one of these causes and discuss which foods are likely to be beneficial.

Is There a Web Site that Lists Ongoing Clinical Trials for WM?

The NCI maintains a web site that contains fully searchable information about every NCI-sponsored clinical trial for WM and other cancers. It can be accessed at: http://www.cancer.gov/clinicaltrials/search/ (See **Resources and Links**).

For questions, please feel free to contact us at:

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Resources and Links

Federal Government Sites

National Cancer Institute Information Line:
http://www.cancer.gov

1-800-4-CANCER
This resource, sponsored by the National Cancer Institute (NCI), provides information on current research for a variety of cancer sites. It provides a searchable index of *all NCI-supported clinical trials* for WM and other cancers. It also discusses a variety of cancer-related topics in lay terms. It is an excellent resource for patients and oncologists who wish to explore the availability of clinical trials testing new treatments for different cancers.

National Human Genome Research Institute:
http://www.genome.gov/Education/

The National Human Genome Research Institute (NHGRI) is a component of the National Institutes of Health. NHGRI maintains an Educational Resources page on its web site that is devoted to providing information about concepts related to genetics, a glossary of genetic terms, and more. While not strictly related to WM, it provides a user-friendly way to learn about the general topic of genetics.

PubMed Central:
http://www.pubmedcentral.nih.gov/

PubMed Central, a service of the National Institutes of Health (NIH), provides free digital archives of biomedical and life sciences journal literature. A search of PubMed Central will provide the citations for relevant publications. The citation may contain a link to the actual article if the publisher has agreed to make the article available to the public.

My Family Health Portrait
https://familyhistory.hhs.gov/

My Family Health Portrait is a web-based tool that makes it easy for you to record your family health history. The tool allows you to assemble your information and makes a "pedigree" family tree that you can download to share with family members or your healthcare practitioner. The Web site only provides the software for organizing your information. By accessing the tool on the web, you make use of that software. The information you fill in is never available to anyone else, unless you decide to share it.

We are providing links to other Internet sites for informational purposes and for your convenience.

Non-Federal Sites*

American Cancer Society:
http://www.cancer.org

The American Cancer Society (ACS) provides information and resources for cancer patients nationwide, as well as funding for clinical and basic research in all aspects of cancer biology and treatment.

American Society of Clinical Oncology:
http://www.cancer.net

The American Society of Clinical Oncology (ASCO) provides oncologist-approved information and resources for cancer patients and their caregivers. It includes information on national policy, guides to specific cancer types, and resources for understanding and managing costs of cancer care and coping with the impact of a cancer diagnosis.

International Waldenström Macroglobulinemia Foundation (IWMF):
http://www.iwmf.com

IWMF provides information, resources, a communications network, and experience on how to live with WM, as well as mutual support among individuals who have WM and their caregivers. There are members and local area support groups worldwide. IWMF sponsors an annual patient education forum each spring. IWMF also encourages and funds research toward more effective treatment of WM.

*We are providing links to other Internet sites for informational purposes and for your convenience. Please note the following:

1. When you select a link to an external Web site, you are leaving the NCI Web site and you are subject to the privacy and security policies of the owners/sponsors of the external site.

2. NCI does not endorse organizations that sponsor linked external Web sites. In addition, NCI does not endorse products or services that such organizations may offer. Furthermore, NCI does not control or guarantee the currency, accuracy, relevance, or completeness of information found on linked, external Web sites.

3. NCI is not responsible for transmissions users may receive from linked, external Web sites.

4. NCI does not guarantee that linked, external Web sites comply with Section 508 (Accessibility Requirements) of the Rehabilitation Act.

The Waldenström Macroglobulinemia Family Study Team

Mary L. McMaster, M.D., is the Lead Investigator of our study. Dr. McMaster is responsible for developing and leading the study. She trained in medical oncology at Vanderbilt University and in medical genetics at the National Human Genome Research Institute before coming to the National Cancer Institute (NCI). She is an expert in familial WM and WM precursor disorders. She has been studying patients with familial WM for over 10 years. She was a founding member of the International Waldenström Macroglobulinemia Workshop in 2000. She has also worked closely with the International Waldenström Macroglobulinemia Foundation to raise awareness about familial WM.

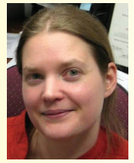
Terri Giambarresi, B.S.N., R.N., G.C.N., is our primary Research Nurse. She is your first line of communication and information about the study. Terri will work with you on putting together your family history information and in organizing visits to our clinics and coordinating medical tests.

Linda Vasquez, A.A., R.N., is a Clinical Research Specialist who assists Terri and Dr. McMaster in coordinating all the details of the study. Along with Terri, Linda assists patients and family members who come to the NIH Clinical Research Center for evaluation.

Lynn Goldin, Ph.D., is a Genetic Epidemiologist on the study. Dr. Goldin trained at the University of North Carolina at Chapel Hill. Her major research interests are in developing and evaluating statistical methods and study designs for detecting susceptibility genes for complex diseases, quantifying how diseases cluster in families, and applying these methods to familial cancer studies.

Comings and Goings

Deborah Colby, M.A., has assumed the role of Research Assistant for the study. She has a B.A. in psychology from the University of Maryland, Baltimore County and an M.A. in experimental psychology from Towson University. She helps the study to run smoothly by assisting Terri and Linda and maintaining and managing study records.



Jill Koshiol, MSPH, Ph.D., has joined the study team as a Cancer Epidemiologist. Dr. Koshiol trained in epidemiology at the University of North Carolina at Chapel Hill. She is interested in infections that cause cancer. She is particularly interested in why immune-related conditions, such as certain autoimmune diseases and infections, seem to increase risk of WM.

Ruth Pfeiffer, Ph.D., has joined us as our study's Statistician. She is helping us develop the statistical methods for our new analyses. Dr. Pfeiffer received her Ph.D. in mathematical statistics from the University of Maryland, College Park. Her research focuses on statistical methods for problems arising in genetic epidemiology.

Ola Landgren, M.D., trained in hematology and internal medicine at the Karolinska Institute (Stockholm, Sweden). In 2004, he came to the National Cancer Institute, Genetic Epidemiology Branch, DCEG, where he worked as an Investigator before he joined NCI's Medical Oncology Branch. His research interest is in the natural history of the precursor condition, monoclonal gammopathy of undetermined significance (MGUS), and its relationship to WM. We collaborate with him on various aspects of the study.

Veda Byrd, B.S., who worked with many of you in the study, left the NCI to enter a graduate program in public health. We know that you join us in wishing her the best of luck in her studies.

Glossary — Words to Know

We have provided a list of definitions of some of the genetic and technical terms that will make this newsletter easier to understand.

affected – An individual in a pedigree or family who has the condition that is being studied.

allele – An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. Different alleles produce variation in inherited characteristics such as hair color or blood type.

anemia – A condition in which the number of red blood cells is below normal. Red cells are the cells that carry oxygen from the lungs through the bloodstream to other organs throughout the body.

autoimmune disease – A condition in which the body mistakenly recognizes its own tissues as foreign and directs an immune response against them. Patients with autoimmune diseases frequently have unusual antibodies circulating in their blood that target their own body tissues.

autosomal – Refers to any of the chromosomes numbered 1 – 22 or the genes on chromosomes 1 – 22. This term excludes the sex-determining chromosomes, X and Y.

benign – A tumor that grows but does not invade nearby tissues or spread to distant tissues.

B-lymphocyte – (see lymphocyte)

cancer – A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Leukemia is a cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Also called malignancy.

cancer screening – Checking for disease when there are no symptoms. Since screening may find diseases at an early stage, there may be a better chance of treating the disease. Examples of cancer screening tests are the mammogram (breast), colonoscopy (colon), Pap smear (cervix), and PSA blood level and digital rectal exam (prostate). Screening can also include checking for a person's risk of developing an inherited disease by doing a genetic test.

candidate gene – A candidate gene is a gene whose chromosomal location is associated with a particular disease or other phenotype. Because of its location, the gene is suspected of causing the disease or other phenotype.

chromosome – One of the threadlike "packages" of genes and other DNA in the nucleus of a cell. Except for sperm and eggs, all human cells contain 46 chromosomes that occur in 23 pairs: 2 pairs of each of the 22 autosomes, plus either two X chromosomes (females) or an X and a Y chromosome (males).

clone – Cells that are derived from a single common ancestor cell. Clonal cells are a group of cells of the same type that are genetically identical. Cells from a single clone are called monoclonal.

cytogenetics – The study of chromosomes and chromosomal abnormalities.

deletion – The loss of all or a part of a gene. There may also be a change in the RNA and protein made from that gene. Certain gene deletions are found in cancer and in other genetic diseases and abnormalities.

disease-causing mutation – A gene change or alteration that causes or predisposes an individual to develop a specific disease.

DNA – The molecules inside cells that carry genetic information and pass it from one generation to the next. Also called deoxyribonucleic acid.

electrophoresis – A laboratory test used to separate substances, such as proteins, based on the rate of movement of each component while under the influence of an electric field. Proteins can be identified because they move at a predictable rate based on their physical and electrical properties. Electrophoresis is commonly performed on serum or urine. After the proteins have been separated, they are identified using special stains. There are two major methods used for this process, immunoelectrophoresis and immunofixation electrophoresis.

epidemiology – The study of the patterns, causes, and control of disease in groups of people.

familial cancer – Cancer that occurs in families more often than would be expected by chance. These cancers often occur at an early age and may indicate the presence of a gene mutation that increases the risk of developing cancer. They may also be a sign of shared environmental or lifestyle factors.

family history – A record of the relationships among family members along with their medical histories. This includes current and past illnesses. A family history may show a pattern of certain diseases in a family. Also called family medical history. When represented in diagram form using standardized symbols and terminology, it is usually referred to as a pedigree or a family tree.

first-degree relative – The parents, brothers, sisters, or children of an individual.

gammopathy – A disturbance in the production of immunoglobulins. Immunoglobulins are in the group of plasma proteins that are known as the gamma globulins, hence the term "gammopathy."

gene – The functional and physical unit of heredity that is passed from parent to child. Genes are pieces of DNA, and most genes contain the information for making a specific protein. The proteins are responsible for specific characteristics or functions within a cell. Every gene occupies a specific location (or locus) on a chromosome.

genetic disorder – Disease that is caused by an abnormality in an individual's DNA. Genetic disorders are inherited (passed from parent to child) only if the abnormality is present in the germline.

genetic counseling – A communication process between a specially trained health professional and a person concerned about the genetic risk of disease. The person's family and personal medical history may be discussed, and counseling may lead to genetic testing. Genetic counseling provides affected or at-risk individuals and families with information about their condition and helps them make informed decisions about their medical care.

genetic marker – An alteration in DNA that may indicate an increased risk of developing a specific disease or disorder. An identifiable segment of DNA with enough variation between individuals that its inheritance along with alleles of a given gene can be traced; used in linkage analysis.

genetic predisposition – An inherited increase in the risk of developing a disease. Also called genetic susceptibility.

genetic screening – Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. Also called genetic testing.

genome – The complete genetic material of an organism.

germline – The DNA in germ cells (egg and sperm cells that join to form an embryo). Germline DNA is the source of DNA for all other cells in the body; can be passed from parent to child.

germline mutation – A gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring (child). Germline mutations are passed on from parents to child. Also called hereditary mutation.

hyperviscosity syndrome – A clinical condition caused by an abnormal sluggishness of blood flow through peripheral vessels, caused by the accumulation of large proteins, such as immunoglobulins, in the serum; increased viscosity may trigger bleeding from mucous membranes, blurred vision, headache, dizziness, and neurological symptoms.

IgM – One of the five classes of immunoglobulins; also known as macroglobulin. It differs from other immunoglobulin molecules in being five times the size of standard-sized immunoglobulin.

immunoglobulin – A protein that acts as an antibody. Immunoglobulins are made by B-cells and plasma cells. An immunoglobulin is a type of glycoprotein with two heavy chains and two light chains. Immunoglobulins play an essential role in the body's immune system. They identify and attach to foreign substances, such as bacteria, and assist in destroying them. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM. Immunoglobulins are made up of a mixture of two types of protein chains. The larger of the protein chains is called the heavy chain and the smaller is called the light chain. There are two types of light chains, called kappa and lambda. A given immunoglobulin will have only one type of heavy chain and one type of light chain. Abbreviated as Ig.

inherited – Transmitted through genes that have been passed from parents to their children.

kindred – An extended family.

leukemia – A cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

linkage – The close association of genes or other DNA sequences on the same chromosome. The closer two genes are to each other on the chromosome, the greater the probability that they will be inherited together.

linkage analysis – A gene-hunting technique that traces patterns of disease in high-risk families by identifying genetic markers of known chromosomal location that are inherited along with the trait or disease of interest.

lymphocyte – A type of immune cell that is made in the bone marrow and is found in the blood and in lymph tissue. The two main types of lymphocytes are B-lymphocytes (also called B-cells) and T-lymphocytes. B-lymphocytes make antibodies, and T-lymphocytes help kill tumor cells and help control immune responses. A lymphocyte is a type of white blood cell.

lymphoma – Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is non-Hodgkin lymphoma, which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. These subtypes behave and respond to treatment differently. Both Hodgkin and non-Hodgkin lymphomas can occur in children and adults, and prognosis and treatment depend on the stage and the type of lymphoma.

malignancy – Another term for cancer. A malignant tumor can invade nearby tissues and has the ability to spread to distant tissues through the bloodstream or lymph system.

mode of inheritance – The manner in which a genetic trait or disorder is passed from one generation to the next. Autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, multifactorial, and mitochondrial inheritance are examples. Each mode of inheritance results in a characteristic pattern of affected and unaffected family members.

monoclonal – A group of cells that are all identical copies of an original cell. Such a population of identical cells is called a clone, and monoclonal means a single clone. All tumors, both benign and malignant, are monoclonal, that is, they are the result of the transformation of a single cell. That single cell multiplies and forms the tumor.

monoclonal gammopathy – The production and presence in the blood and/or urine of a protein called a monoclonal immunoglobulin. The monoclonal immunoglobulin results from the transformation of a single B-lymphocyte or its derivative cell, the plasma cell. This protein is in the group of plasma proteins that are known as the gamma globulins. Hence, the term "gammopathy." Also called M-protein or M-spike.

monoclonal gammopathy of undetermined significance (MGUS) – A benign condition in which there is a higher-than-normal level of a protein called immunoglobulin, or M-protein, in the blood. Patients with monoclonal gammopathy of undetermined significance are at an increased risk of developing certain types of cancer. Also called MGUS.

multiple myeloma – A type of cancer that begins in plasma cells (white blood cells that produce antibodies).

mutation – Any change in the DNA of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they are present in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

neutropenia – A condition in which there is a lower-than-normal number of neutrophils (a type of white blood cell).

pedigree – A diagram that shows relationships among family members. In medicine, a pedigree may also show the pattern of certain genes or diseases within a family.

phenotype – The observable physical or laboratory characteristics in an individual that result from the expression of a gene or set of genes; the clinical presentation of an individual with a particular genetic background. In WM families, WM and IgM MGUS are two of the most important phenotypes.

platelet – A tiny piece of a cell found in the blood that breaks off from a large cell found in the bone marrow. Platelets help wounds heal and prevent bleeding by forming blood clots. Also called thrombocyte. If the platelet count in the blood is lower than normal, the patient is said to have thrombocytopenia.

Glossary — Words to Know (continued)

polyclonal – Descended from more than one group of cells, especially of genetically different origins (as opposed to monoclonal).

precursor condition – A condition that can lead to development of a particular cancer or disease. A precursor condition usually affects the same type of cells and is in the same location as the cancer that eventually develops. The cells in the precursor condition are usually atypical but are not malignant. A precursor condition does not necessarily develop into a cancer and may disappear (regress) in time. To develop cancer, the precursor cells must accumulate a series of damaging genetic changes. If these changes do not occur, cancer will not develop.

risk assessment – The evaluation of an individual's risk of carrying a certain gene mutation, or developing a particular disorder, or of having a child with a certain disorder; this is sometimes done by using mathematical or statistical models including such factors as personal health history, family medical history, and ethnic background.

risk factor – Something that may increase the chance of developing a disease. Some examples of risk factors for cancer include age, a family history of certain cancers, use of tobacco products, certain eating habits, obesity, lack of exercise, exposure to radiation or other cancer-causing agents, and certain genetic changes.

second-degree relative – An aunt, uncle, grandparent, grandchild, niece, nephew or half-sibling of an individual.

sporadic – A disease or condition that occurs in a patient who has no family history of the disease or condition. Also known as nonfamilial.

susceptibility gene – Inherited factor that predisposes a person to a certain disease or disorder. A gene having a germline mutation that increases an individual's predisposition to a certain disease or disorder. When such a mutation is inherited, development of the illness is more likely, but not 100% certain. Also called a predisposing (disease-related) mutation.

thrombocytopenia – A condition in which there is a lower-than-normal number of platelets in the blood. It may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues.

unaffected – An individual who does not have the condition or disease that is occurring in his or her family.

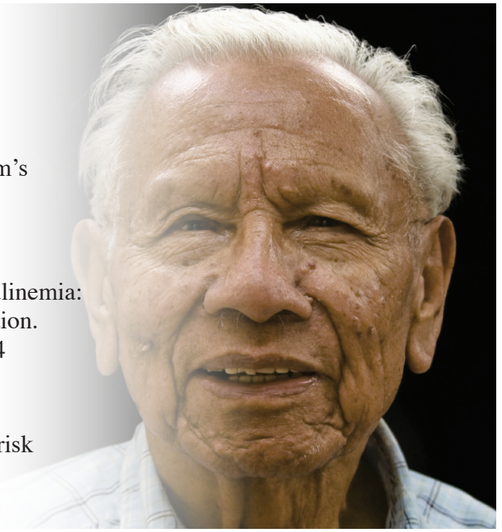
Waldenström macroglobulinemia (WM) – An indolent (slow-growing) type of non-Hodgkin lymphoma in the bone marrow marked by increased levels of IgM antibodies in the blood and an enlarged liver, spleen, or lymph nodes. Also called lymphoplasmacytic lymphoma. Symptoms can be caused by either the lymphoma cells (for example, low blood counts) or the IgM (which may mistakenly attack normal body cells, such as platelets). When levels of IgM are extremely high, the blood may become excessively viscous ('sluggish' or 'thick'), leading to hyperviscosity syndrome.

white blood cell – A type of immune cell. Most white blood cells are made in the bone marrow and are found in the blood and lymph tissue. White blood cells help the body fight infections and other diseases. Granulocytes, monocytes, and lymphocytes are white blood cells. Also called leukocyte and WBC.

For definitions of genetic terms that do not appear on this list, please refer to the online glossary of terms provided for patients by the NCI: http:// www.cancer.gov/cancertopics/genetics-terms-alphalist and by the National Human Genome Research Institute: http:// www.genome.gov/glossary.cfm.

The "typical" WM patient is diagnosed at about age 70.

Medical Articles



The following published articles give more detail on the studies described in this newsletter:

Page 2, Features of Familial WM Familial Waldenström's macroglobulinemia. *Seminars in Oncology*, 2003, Volume 30, pages146-152

Page 3, Searching for WM Genes — Cytogenetics Cytogenetics of familial Waldenstrom's macroglobulinemia: in pursuit of an understanding of genetic predisposition. *Clinical Lymphoma*, 2005, Volume 5, pages 230-234

Page 4, Searching for WM Genes — Linkage study Genetic predisposition in familial Waldenström macroglobulinemia: a genome-wide search of high-risk families provides evidence of susceptibility loci on chromosomes 1 and 4. *American Journal of Human Genetics*, 2006, Volume 79, pages 695-701

Page 5, Searching for WM Genes — Candidate genes Common genetic variants in candidate genes and risk of familial lymphoma. *British Journal of Haematology*, 2009, Volume 146, pages 418-423

Page 5, Precursor Conditions for WM Waldenström macroglobulinaemia and IgM monoclonal gammopathy of undetermined significance: emerging understanding of a potential precursor condition. *British Journal of Haematology*, 2007, Volume 139, pages 663-671

Page 6, Studies of WM and B-cell Cancers in the General Population Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia patients: a population-based study in Sweden. *Blood*, 2008, Volume 112, pages 3052-3056

Page 7, Influence of Race on Risk for WM Prevalence of monoclonal gammopathy of undetermined significance among adult males in Ghana. *Mayo Clinic Proceedings*, 2007, Volume 82, pages 1468-1473

Page 7, Chronic Immune Stimulation and Risk for WM Chronic immune stimulation and subsequent Waldenström macroglobulinemia. *Archives of Internal Medicine*, 2008, Volume 168, pages 1903-1909

Below are some other articles that we have published about WM.

1. Protein electrophoresis, immunoelectrophoresis, and immunofixation electrophoresis as predictors for high-risk phenotype in familial Waldenström macroglobulinemia. *International Journal of Cancer*, 2008, Volume 122, pages 1183-1188
2. Long-term follow-up of three multiple-case Waldenström macroglobulinemia families. *Clinical Cancer Research*, 2007, Volume 13, pages 5063-5069
3. Novel aspects pertaining to the relationship of Waldenström macroglobulinemia, IgM monoclonal gammopathy of undetermined significance (MGUS), polyclonal gammopathy and hypoglobulinemia. *Clinical Lymphoma and Myeloma,* 2009, Volume 9, pages 19-22
4. Genetic and immune-related factors in the pathogenesis of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. *Clinical Lymphoma and Myeloma*, 2009, Volume 9, pages 23-26