

## Read This First

Most of us get our health information from magazines, TV news, and the Internet. We don't usually read scientific or medical journals. Therefore, we offer you this **Research Report** in plain English.

### ***What causes lymphoma?***

It would be so much easier if "somebody" could just "do a big study" and "find the answer" to the question of what causes lymphoma. Both fortunately and unfortunately, that isn't the way science works. One study doesn't usually "prove" anything. Instead, scientific knowledge develops by careful testing and retesting of theories through a gradual collection of evidence.

When a scientific study is finished, the most that can be claimed is that a statistical association between one or more factors and a certain outcome has been found — an association, but not necessarily the cause.

Of course, important breakthroughs do occur, and some research studies are better designed and produce more meaningful results than others. Still, any study that shows an association between factors must be reproduced by other scientists working independently, before the theory which is being tested gains favor in the scientific community.

### **What "Causes" Cancer?**

All of us define "cause" differently, depending on whether we are considering "cause" from a medical, legal, religious, or everyday perspective. The definition of "cause" and the whole idea of causation are rarely mentioned by cancer researchers.

Common sense tells us that the cause of an event or an effect may be complex or unknown. In reading and evaluating research study results, we need to give some thought to the different definitions of "cause" and to the ways the author's point of view can affect research methods.

**Question:** Why does food get moldy after being left out on the kitchen counter for a few days?

**Answer:** Ask several people and you'll get several answers:

- Because mold is everywhere;
- Because a few days is too long to keep food at room temperature;
- Because Annie didn't cook it thoroughly;
- Because Jack didn't clean the countertop;
- Because the weather was hot and humid.

Of course, there may be other theories of what "causes" mold to grow. Any of them might be involved in the spoiled food problem. Obviously, your understanding of the "true cause" will depend to some extent upon your level of knowledge concerning mold growth, your experience with food preparation and storage, and whether you are Annie or Jack.

***Your ideas about cancer may depend on whether you're a cancer patient, doctor, researcher or chemical company.***

In that same way, your understanding of what causes cancer may depend on your knowledge of the ways in which cancer develops, as well as whether you are a cancer patient, friend of a cancer patient, cancer doctor or researcher — or a manufacturer of pesticides.

One of the most publicized stories about the "cause" of cancer is the ongoing drama of the cigarette companies and their attempts to show, in extended legal battles, that people develop lung cancer not from smoking, but from their own inherent problems and weaknesses.

You, the reader, need to understand that when lymphoma is discussed by researchers, there are many things to consider: heredity, viruses, our exposure to chemicals, and toxic substances in our air, water, and food. These factors and exposures may vary, depending in part on our chosen occupations and where we live. Any or all of these may weaken a person's immune system. These are only some of the possible — even probable — "causes" of cancer. It appears that pesticides may be one piece of a larger lymphoma puzzle.

Two studies in our **Research Report** (Faustini, 1996 and Figs, 1998) show that exposure to 2,4-D (a commonly used weed killer) killed large numbers of lymphocytes in the people who were studied. These people's immune systems were weakened.

***These people's immune systems were weakened.***

Their lymphocyte counts improved only slowly. When the body is forced to form new lymphocytes after this kind of toxic injury to the immune system, mutated, abnormal cells may form in some cases, leading to the development of lymphoma.

As is typically the case when a question is studied for many years, there is some disagreement among authors of lymphoma/pesticides studies. Different scientists may look at the same statistics and conclude either “significant association,” “limited evidence,” or “no clear evidence.”

You should be aware that some people are motivated to see “failure to prove cause” unless everyone, or almost everyone, who is exposed to a substance later develops cancer. For example, since cigarette smoking does not cause cancer as reliably as, say, smallpox virus produces smallpox, there are those who will say that cigarette smoking has little or no role in causing cancer. Jonathan Haar’s book, *A Civil Action*, shows how some companies (and their scientists and lawyers) are motivated to “disprove” that chemicals cause cancer.

### **Research Methods: Do They Matter?**

There are many different ways to do research studies. When we read the results of a study, we should look carefully at how the study was designed, carried out, and interpreted. Common sense tells us that a report which mentions only a few cases, occurring in one region within a limited time period, is only suggestive of a pattern, while a study with thousands of people observed over many decades has more power to show meaningful associations.

Here’s what we looked for:

- ✓ Diagnosis of lymphoma must be accurate;
- ✓ Method of assessing exposure to the pesticides must be valid;
- ✓ Exposed populations and control groups must be the same except for their exposure to the pesticide;
- ✓ The number of people studied must be sufficiently large;
- ✓ Analyses and interpretation of results must be appropriately done.

When scientists study people in a particular occupation, there may be unidentified factors and/or exposures that confound the results.

Differences like these may affect a study's outcome:

- Farmers are exposed to sunlight, dusts, machinery, fuel, fumes, and animals, in addition to pesticides.
- With rare exceptions, studies fail to include any women.
- Though the latency period for lymphoma may be very long — easily 20 years after chemical exposures — some studies proclaim findings after only a few years.
- Mortality studies, which include only lymphoma deaths, ignore lymphoma survivors who are receiving treatment or who are in extended remission, and who may have different histories of pesticide exposure than those who have died.
- Some researchers carefully determine a person's exposure to potentially cancer-causing substances or factors. Other researchers use general categories, such as persons employed in a particular industry or living in a certain location.

### **Who Employs the Researchers? Who Pays For the Research?**

While scientists may strive to remain impartial and unattached, they are human. So we need to consider: Who employs the researchers? Who is paying for the research? Naturally, these two questions are closely related.

***The results are likely to differ depending on who is funding the research.***

This idea — that the results of scientific research are likely to differ depending upon who is funding the research — is not just conjecture. A team of researchers who analyzed 70 articles concerning calcium-channel blocking drugs found a very close

relationship between the authors' financial ties and their attitudes toward the drugs. In fact, 100% of those supporting the drugs had financial ties to drug companies, while only 43% of those critical of the drugs had such ties. There was a group who were considered "neutral" (neither for nor against the drugs), and of this group, 67% had drug company ties. Finally, it was discovered that in only 2 of the 70 articles did the authors disclose their corporate/drug company affiliations. ("Conflict of interest in the debate over calcium-channel antagonists," *New England Journal of Medicine*, Vol. 338, No. 2, pp. 101–106.)

Though some scientific and medical journals do show sources of research funding, this practice is not universal. In addition, there may be indirect sources of financial support which are not disclosed in such listings. In our **Research Report**, we have listed the authors' stated institutional/organizational affiliations and, when shown, funding sources. Since our information comes solely from the journal articles, we have no way of knowing all the affiliations nor funding sources of the authors, nor whether some have financial ties to the industries whose chemicals they are studying.

Even in instances where funding is available with few strings attached, there is a scientific "culture" that limits the types of research likely to be carried out by an agency or the scientific community as a whole. Also, studies with a "positive" result are more likely to be published than studies that don't show a correlation between the factors studied, even though a lack of findings is also an important piece of scientific evidence when a study is well-designed and well-executed.

Over the last 30 years there has been much more scientific interest in cancer chemotherapy, surgery, transplantation, immune therapies, and radiation than in alternative approaches, despite the public's great interest in them. The large role of drug companies in the funding of research may be part of the reason why so little money is spent on true cancer prevention (as opposed to detection) and the study of alternative treatments.

### **Hidden Bias**

In November, 1997, the prestigious *New England Journal of Medicine* published an extremely negative review of a book written by Sandra Steingraber, *Living Downstream: An Ecologist Looks At Cancer and the Environment*. In that book, Dr. Steingraber cites evidence that the increase in lymphoma may be related to pesticides exposure. Why was the reviewer so highly critical of the book? Did he have a hidden bias?

The next month, the *New England Journal of Medicine* apologized publicly for failing to inform readers that the author of that negative book review was the medical director of W.R. Grace & Co., a Massachusetts corporation that had received extensive negative publicity for polluting ground water that may have contributed to higher than expected rates of leukemia among nearby residents.

### **Are Some Studies Better Than Others?**

Some studies really are better than others. *Differences in study design are important.* Larger studies and those involving longer time periods may be more meaningful. The way a study is designed and carried out is critical.

Among the thousands of studies and articles which are published each year, not all bear the same weight or have equal influence in the scientific community nor in the public understanding. Those published in more prestigious journals are more widely read and respected.

Studies that are more highly publicized, or which catch the attention of the press because they address an interesting subject (like obesity or impotence), or are released on a day when there is little other news, get more publicity than others. That doesn't necessarily mean that they are more important or that we should base our decisions on what we read or hear in the news.

There are also differences among studies done in various countries. The conditions under which scientists work are not all the same. In some countries, especially in Northern Europe, extensive record keeping is required of all citizens and businesses, which gives scientists access to fairly accurate records showing which people worked where and under what conditions. Certain countries, such as Sweden, maintain national cancer registries which provide information on all cases and all types of cancer. This information can make it much easier for scientists working in these countries to obtain complete information about the people they are studying.

## 12 Words You Need to Know

### 1 Pesticide

A substance used to kill or reduce the numbers of unwanted forms of life in a particular environment. These life forms may be unwanted plants (“weeds”), fungi, insects, or animals such as rats. Most pesticides are man-made chemicals, though a few are naturally derived from plants. Though efforts are made to choose pesticides which are toxic only to the intended target and not to humans or other living things, often pesticides have more general toxicity. Pesticides are widely used in schools, factories, offices, homes, public and private lands, and in farming. The use of pesticides has greatly increased in recent times. Many pesticides persist in the environment and can be found in air, water, soil, plants and animals (including the food we eat), and in our own bodies.

### 2 Herbicide

A substance used to kill plants. Some herbicides kill all plants with which they come into contact; these are often called defoliant. Others are more specific, affecting only certain types of plants, such as crabgrass or plants that are not grasses. Herbicides are used widely in home lawn care, farming, and for weed control in public areas (parks, streets, golf courses, and highway areas).

### 3 Fungicide

A substance used to kill fungi (“funguses”). Yeasts, molds, mildew, and mushrooms are examples of fungi.

### 4 Insecticide

A substance used to kill insects. These are very widely used in nearly every kind of human environment, including homes, gardens, apartment buildings, schools, office buildings, restaurants, bakeries, and farms. They are also applied directly on adults, children, and pets. The term “insecticide” is sometimes used when the target is not, strictly speaking, insects, for example, worms.

**5 Carcinogen**

A substance that causes cancer. “Carcinogenic” means “causing cancer.”

**6 Chlorophenol**

A type of manmade chemical that contains chlorine atoms and a ring-shaped carbon structure. Chlorophenols have some similarity to naturally-occurring substances, except for the chlorine atoms. These chemicals are toxic to living organisms, even in tiny concentrations. Chlorophenols vary in their nature, uses, toxicity, and tendency to cause cancer.

***These chemicals are toxic to living organisms, even in tiny concentrations.***

The phenoxy herbicides, frequently mentioned in our **Research Report**, are chlorophenols. So are DDT, PCB, TCDD, and many other chemicals now or formerly used in

farming, landscaping, industrial processes, and home, school, and office pest control. These chemicals are sometimes called chlorinated (or halogenated — refers to the group of elements that includes chlorine) hydrocarbons, or organochlorines.

Even people who don't use these substances in their work may be exposed to them through drinking water, food, pesticide sprays used at home, school, work, home or business landscaping, and use on public lands such as parks and along highways. All people living in industrialized nations are exposed to these chemicals. We have residues of them in our body's own body fat, where such chemicals tend to persist. (See *dioxin/TCDD*, below)

**7 Dioxin/TCDD**

TCDD is 2,3,7,8-tetrachlorodibenzo-p-dioxin, also just called “dioxin.” The numbers refer to the locations on the carbon structure where the four chlorine atoms are located. The term “dioxin” can also be applied to closely related chemicals.

One of the most toxic chemicals known, TCDD/dioxin occurs as a contaminant/byproduct when certain pesticides are manufactured.

It also gets into the air from incineration of chemical wastes and from certain industrial processes. Dioxin persists in the environment, breaks down very slowly, and tends to become concentrated in the fatty tissues of living animals and humans.

***Unfortunately, we all have residues of chlorophenols in our own body fat.***

Fish living in dioxin-contaminated waters contain much higher concentrations of dioxin than the water does.

Americans get 90% of their dioxin exposure by eating dairy products, meat, and fish. Since dioxin is concentrated in fatty tissues, it occurs in human breast milk. According to Dr. Sandra Steingraber, "a breast-fed infant receives its so-called "safe" lifetime limit of dioxin in the first six months of drinking breast milk." (Raffensperger, C. & Tickner, J., eds. *Protecting Public Health and the Environment*, Island Press, Washington, DC).

Dioxin is also a hormone disruptor, even in concentrations much smaller than those that can cause cancer. Other health problems which some experts believe are linked to widespread dioxin contamination include the international epidemic of lowered sperm counts, the increase in breast cancer, and learning disabilities in children.

### **8 Case-control study**

A study in which "cases" ( people who have a disease) are compared with "controls" (people who don't have the disease). The differences between the two groups might reveal the cause of the disease. In our **Research Report**, "cases" are people with lymphoma; "controls" are people with no lymphoma. In designing a case-control study, scientists may consider such variables as age, gender, residence, occupation, race, military duty, etc. Sometimes several controls are selected for each case. Often the controls are selected at random from the same general population (hospital, state, etc.) where the cases are found. Good choice of cases and controls is a very important part of the design of all case-control studies.

**9 Cohort study**

A defined group of people (cohort) is followed up over time to observe their incidence of (or mortality from) a disease. The incidence or mortality in the cohort is compared either to the general population or to persons lacking the characteristic or exposure being studied.

**10 Mortality study**

A study of deaths from a particular disease (non-fatal cases are left out). A mortality study may have a cohort or case-control design. There is a weakness in the use of mortality studies for lymphoma, because many cases of lymphoma are not fatal. Since lymphoma survivors are ignored, the occurrence of lymphoma can appear lower than it really is.

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In some populations, exposure to carcinogens may increase the incidence of lymphoma at a relatively young age, resulting in higher than expected incidence but few deaths, since younger patients may better tolerate cancer treatments.

Differences in access to treatment may affect mortality, and may differ from risk factors which affect incidence. Also, the cause of death recorded on a certificate sometimes does not reflect underlying illness. For instance, a death certificate may show the cause as kidney failure, but the kidney failure may have resulted from cancer chemotherapy. Still, mortality studies do provide useful information.

In the United States, it is often easier to conduct mortality studies than incidence studies because death records are easier to obtain than information about disease incidence. Norway, Finland, and England have complete records of every cancer case in their countries, making mortality studies less attractive as a study design (and incidence studies easier to carry out). These nations also have very complete data on the occupations of their citizens, which researchers can fairly easily match with cancer data for individuals.

**NOTE:** We have not attempted to define all types of study designs, but only to explain some of those which occur frequently in our

**Research Report.** For example, in a **meta-analysis**, a group of similar studies is evaluated for possible patterns or results not obtainable from the studies separately.

**11 Odds ratio (OR)**

Simply put, a measure of the risk of cancer for a study population (people exposed to a pesticide) divided by the risk for a population lacking the characteristic or exposure being studied (people not exposed to the pesticide). The odds ratio shows whether the group under study has more, less, or about the same chance of getting the disease as people who are not exposed to the pesticide.

**12 Standard incidence ratio (SIR) and standard mortality ratio (SMR)**

These, like the odds ratio, are ways of expressing the relationship of incidence (or mortality) from lymphoma in a study population to that in a reference group, except that in this case, the reference group is the whole population (of one country, usually).

Here's an example using *mortality figures*: Employees in certain pesticide factories had a SMR of 3.26 for non-Hodgkin's lymphoma. This means that 3.26 times as many people in that population died from non-Hodgkin's lymphoma as would have in a sample of the same size taken from the general population.

Here's an example using *incidence figures*: If in the population of the U.S., 15 cases of non-Hodgkin's lymphoma would be expected per 100,000 person-years, but in a study group of people exposed to a particular pesticide for a total of 100,000 person-years, 30 cases occurred, this would result in a SIR for non-Hodgkin's lymphoma in that group of 2.0 (twice the expected incidence).