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**GUIDE TO
COMPREHENSIVE
CANCER CARE**

**PATIENT / FAMILY
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SELF CARE GUIDES

TESTS & PROCEDURES

**COMPLEMENTARY /
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In the Know

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March 2004

from

The Duke Patient/Family Resource Center

The Duke Patient/Family Resource Center is:

- A lending library offering books, audio and video tapes, magazines and free brochures dealing with cancer and certain blood disorders and with issues of coping, survivorship, caregiving, and grieving
- Open 8:30 to 5:00 every day the Morris Clinics are open
- Located in the White Zone, first floor, of the Morris Cancer Clinic, Room 15123.
- Our phone number is 919-684-6955. Our email address is FamilyLibrary@mc.duke.edu

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Cancer and the Immune System

Imagine you need to hire someone for a very challenging job. The pay will be high, the skills needed impressive. You put out an ad.

Gratifyingly, a virtual army of resumes floods your mail box. Almost all applicants have at least one enthusiastic reference; many have the skills you've been looking for. Surely the right candidate is in this applicant pool somewhere.

But upon closer interviewing and some deep background checking, you discover that:

1. Many will only work in a team of their own choosing – that means hiring the others at equally high pay. You can't afford to take this route. And would the team itself accomplish what you're looking for? Not clear.
2. Quite a few only want to work part-time.
3. Several look great on paper and are terrific test-takers, but faced with the actual job challenge, they fade.
4. A few turn out to be well-intentioned bunglers. While trying to do the job, they actually undermine their own work.

Sound like the average pool of human talent? Actually, the job I'm talking about is fighting cancer and the "applicants" are all components of the human immune system. Cancer research scientists are the folks putting out the ad for job applicants and doing the interviewing and coming up with these frustrating findings. The "high salary" for the right candidate is, of course, the high cost of drug development.

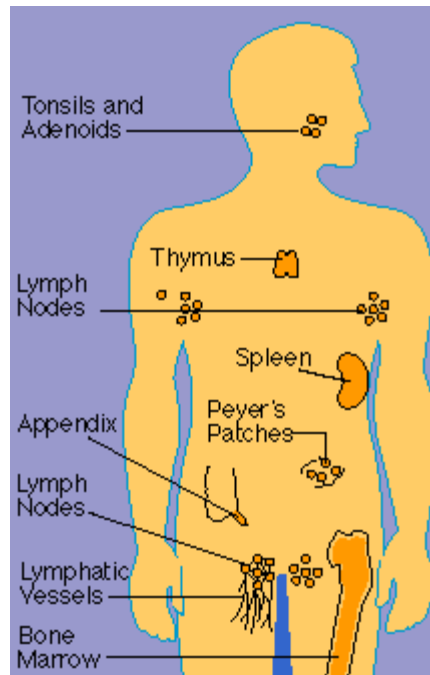
Harnessing the immune system seems, on the face of it, a brilliant idea. The human immune system, consistently praised as a marvel of evolutionary engineering, can do the one thing that most of our chemos and radiations and surgeries cannot do: *precisely locate anywhere in the body* the unwanted cells that are causing the problem and eliminate them. It works its magic on foreign pathogens ("germs") so unobtrusively and consistently that most of us spend most of our lives NOT SICK. When a pathogen comes along to temporarily stump it, e.g. a flu bug it's never seen before, the B cells of the immune system, as they multiply, are actually able to reshuffle their genes and thus mutate themselves until they produce a cell type that works. This new cell type then proliferates and does its work and the patient begins to recover. As recovery proceeds, the immune response quietly shuts itself down – your clogged nasal passages clear, your inflamed wound normalizes, the tooth abscess dries up, etc. A few of those mutated B cells linger in your system to provide a "memory" of the disease. If the disease shows up again, they're right on it before it can get a foothold. You have acquired an immunity to that disease.

Why couldn't these astonishing talents be harnessed by science to combat cancer? Indeed, why aren't they harnessed by the body itself? The puzzling thing about cancer and immunity is that most people with cancer – unless they've been laid low by a heavy

chemo treatment or compromised by HIV – have a functioning immune system. They aren't being attacked by every opportunistic infection that comes their way. Their blood counts are quite normal. When researchers test them with new “antigens” (things that provoke an immune response), their immune response is as good as the control group. Nonetheless, they have cancer. What's going on here?

Do-it-yourself background information

To describe, even in simple terms, the normal workings of the human immune system, would run me out of space before I could get to the questions concerning cancer. What I will do here is refer you to three useful website for introductory information, *if you want it*, then proceed with our discussion at a very general level that you will be able to follow without the background information. Once I turn to specific “immunotherapies” for cancer, I will add a bit more detail.



The organs of the immune system

The useful websites are:

<http://www.stopgettingsick.com/ISS/iss1.cfm> The most comprehensive and clearly written of the three. Long but not rich in graphics. Has one section specifically on cancer.

<http://press2.nci.nih.gov/sciencebehind/immune/immune01.htm> A stripped down version of the above, but with more illustrations.

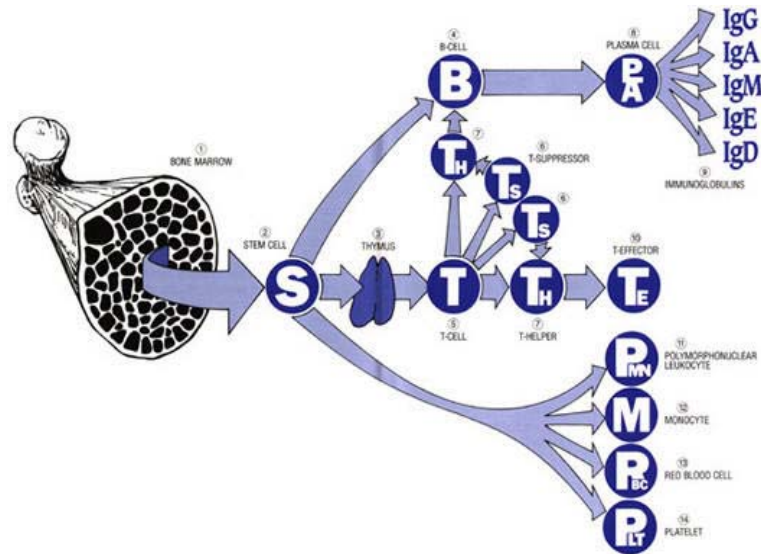
<http://uhaweb.hartford.edu/BUGL/immune.htm#intro> Not clearly written, does not deal directly with cancer, nonetheless it clarifies

some processes the other two sites have skimmed over. Also crammed with weird, interesting facts and figures.

All three sites give one a good basic introduction to the workings of the immune system. The first website (stopgettingsick.com) perhaps best illustrates the immune system's complexity. Try the section called "A billion antibodies." It also contains this wonderful characterization:

"The success of this system in defending the body relies on an incredibly elaborate and dynamic regulatory-communications network. Millions and millions of cells, organized into sets and subsets, pass information back and forth like clouds of bees swarming around a hive. The result is a sensitive system of checks and balances that produces an immune response that is prompt, appropriate, effective, and self-limiting."

As you read on, remember that image of "clouds of bees swarming around the hive." The analogy might be more complete, though the image messier, if one said, "clouds of bees, wasps, hornets, ants and termites." The immune system produces an elaborate genealogy of different cells types, and these organize themselves into teams as they tackle a problem.



The cell subtypes of the immune system and their derivation. The various types of "Ig" are the immunoglobulins, pathogen killing substances secreted by the plasma cells of the immune system.

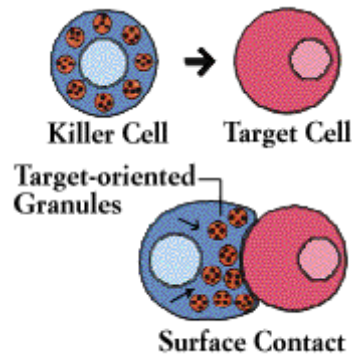
The Theory of Overwhelm

But what does our immune system consider a problem? Let's start with the broad picture. This much we do know about the immune system – that hidden in the complexities of this great evolutionary

achievement lies the answer to two very important questions: Why do some people get cancer? Why doesn't everybody get cancer?

One widely accepted theory is that the immune system is indeed on the job keeping cancer at bay for most people most of the time. Several mechanisms of "tumor surveillance" are at work. The mechanisms of cell repair and programmed cell death ("apoptosis"), discussed in our February issue, may well be the main way that cancer is forestalled, and if we widened our definition of the immune system, these would easily win inclusion. As we have seen, however, cancer cells are mutants that escape these mechanisms. What then?

Of the more familiar parts of the immune system that bear upon cancer, the best known is that subset of "bees" called the "natural killer T cells." These cells patrol the body for any cells that have become too abnormal, whether because of a virus infection or a cancerous change. Unlike many other immune subsets, such as the type of immune cells that go after colds and flu, the natural killer T cells do not need to first figure out the precise identity of their targets; they are innately programmed to respond to generic bad patterns. ("That cell looks like a weirdo, let's snuff him.") They are thus an excellent candidate for the role of tumor surveillance.



The granules inside the killer T cell contain toxins

These kinds of generalized surveillance and repair/elimination succeed in holding cancer in check most of the time. The immune system is not simply in ignorance of the whole problem as some have proposed. It is at work and that is the reason why *not everybody* gets cancer.

There are some catches. But there are some catches. For one, the immune system only has so much energy it can throw into this job. If cancer cells are of the aggressive kind and start proliferating rapidly enough, they will overwhelm the immune system and become entrenched. This is why *some people do* get cancer. In a like fashion, people succumb to infections when the pathogen that has invaded their body is proliferating rapidly enough; infections

can also overwhelm the immune system.

The analogy between infection and cancer is not perfect, however, because an infectious agent that overwhelms is usually proliferating much more rapidly than a cancer that becomes entrenched, but then the two types of disease seem to provoke different levels of immune response.

This leads us to catch number two: most tumors are only weakly provocative to the immune system. This may well be because most cancer cells retain on their surface some of the “self” markers that cause the immune system to tolerate them, if only reluctantly. Researchers have found that many tumors are riddled with immune system cells; when extracted and examined, these cells are found to be doing nothing at all! They showed up for the job, but then faded. That intense cascade of events that germs will set off – the antibody binding to the foreign antigen, the arrival of cytotoxic substances and phagocytes that gobble up intruders, the phagocytes “instructing” the B cells to recognize all of the parts of the vanquished enemy as new antigens – this chain of events seems to fall apart with cancer cells. (“This cell looks like a weirdo, let’s snuff him.” “Nah, he’s one our our guys.” “Really? I’ll just rough him up a little – woops! Hey!”)

Catch number three is that cancer cells can evolve to “hide” their bad patterns. Then the natural killer T cells, those bad pattern spotters, don’t even give them a second glance.

Finally, catch number four, there are those well-intentioned bunglers mentioned above. A number of studies have shown that when inflammation occurs in the region of a tumor, which means that teams of immune cells are rushing to the scene, turning on their cytotoxic chemicals and growth factors and creating a kind of inflammatory soup in the area, this actually helps the tumor to invade the surrounding tissue. Yikes! These disturbing findings have to be balanced against others that indicate an inflammatory response can sometimes defeat cancer. Of those few documented cases of a spontaneous remission of a metastatic cancer, several took place after the patient had weathered a massive infection. We have a book in our collection, *The Transformed Cell*, by Steven A. Rosenberg, that describes one such case. Dr. Rosenberg, the author, who dealt with this case in person, went on to become a famous cancer immunologist.

Age, immunity and cancer. Going back to the theory of overwhelm, we find that if we throw age into the equation, the theory of overwhelm makes even more sense. Remember, we noted in the last newsletter that age is the single biggest risk factor for cancer. Cancer can occur at any age, but the numbers really start to climb as people pass into their 6th, 7th, and 8th decades. One reason

for this, as we discussed last time, is that as time passes, we build up a greater and greater collection of cell mutations and thus increase our chances of having that one mutant cell that spawns a cancer. Now, add the fact that as we age, our immune systems age too. Recall that our normal cells have a limited life-span and the cells of the immune system are no exception. Those bone marrow cells that produce B cells and immature T cells, those thymus cells that complete the manufacture of the T cells, the cells of the lymphoid tissues in our spleens and appendices and throats, etc. - these too begin to dwindle in number as we age. Fewer immune cells translates into less tumor surveillance and this translates into a greater chance that a cancer will become entrenched.

It's relevant to note that when young people do get cancer, it is usually an aggressive form of cancer, one that can prevail against even a high energy immune system. Many of the commonest cancers (lung, colon, breast and prostate) come mainly in sub-types that are just not fast enough to establish themselves in a young person. But in older people, with their low-octane immune systems, these somewhat slower cancers begin to appear. There are certain prostate cancers that are so slow that doctors usually advise the man just to watch it. These typically appear in advanced old age.

Can I keep on smoking, please? There is also substantial variation between individuals. Some people are better endowed with cancer immunity than others. One can always find some heavy smokers, some asbestos workers, some vinyl chloride handlers, even some nuclear blast victims who, despite having sustained massive mutational damage to their cells, nonetheless managed to escape cancer. But don't count on being one of these lucky individuals yourself. Put down the cigarette...

Should I stimulate my immune system with boosters to fight my cancer? If we knew better which parts of the immune system are doing the real cancer fighting, AND how those parts might be stimulated, then the answer might be yes, but just as likely it will be **DO NOT TRY THIS AT HOME**. Some of the immunotherapy achievements that have become part of standard cancer care, such as fighting melanoma and kidney cancer with the stimulating substances that the immune system itself produces (Interferon alpha, Interleukin-2) have revealed that these natural immune products, if administered in quantities sufficient to shrink a tumor, have potentially dangerous side effects. Indeed, the Interleukin-2 treatments have to be administered in the hospital under intensive care monitoring.

Fortunately for our bodies, if not our pocketbooks, the typical "immune boosters" found in health food stores, do little of any significance for cancer. As we'll see below, every one of the tested and sometimes dramatically effective immunotherapies in use today have been created with the tools of biotechnology. There is, at

present, no known herb or non bio-engineered drug that can reach into our immune system and re-orient it in a cancer-fighting direction.

Three Basic Styles of Immunotherapy

Despite my discouraging analogy of the job applicants that introduced this discussion, the field of immunotherapy still holds immense promise and there has been no slacking in the pace of research. There are two principle reasons for this. One is that while only a minority of patients have responded to the tested vaccines and cytokines mentioned below, the response of those few patients has been dramatic. Cancers, even metastatic cancers, in the lucky few have gone away and stayed gone – up to 15 years in certain melanoma patients. For *duration* of response, immunotherapy can hold its head up with the best of known treatments, and for certain cancers such as kidney and melanoma, it is the only known treatment when surgery is no longer an option. The second reason for enthusiasm is the monoclonal antibodies, which have an impressive *rate* of response for a growing selection of the commoner cancers.

There are three basic styles of immunotherapy in use today: vaccines, cytokines, and monoclonal antibodies. The first two styles will have been tested primarily on melanoma, kidney cancer, or brain tumors, as these are the cancers that lack effective chemotherapies. And they will have been tested primarily or exclusively on people with “measurable disease” because the testers need to see if the disease is shrinking. Yet measurable disease usually means a more advanced cancer and thus a tougher challenge for the treatment. Once these same therapies are mass-tested on a wider variety of cancers and especially on people with early cancers or with no detectable disease, just a risk of recurrence, it may emerge that the rate of response to the vaccine and cytokine therapies is greater than thought.

Vaccines: The holy grail of immunology for cancer continues to be the concoction that will permanently wake up the patient’s immune system to the antigens that appear on tumor cells. These are called TAAs or “tumor associated antigens.” An antigen is anything that normally would produce an immune response, but that produces only a weak response, or none at all, in the case of cancer. To engineer around this problem, researchers have tweaked the immune system by presenting tumor antigens in new ways, or beefing up the level of certain of the patient’s immune cells, or throwing an altered virus into the mix to excite immune activity, etc. Every cancer research lab seems to have its own repertory of vaccination home brews that have shown some efficacy. I won’t attempt to describe them. It helps that all cancer cells share certain peptides or proteins that could serve as antigens, thus eliminating the need to tailor each vaccine to each patient. Many trials of

melanoma vaccines are underway across the country.

Cancer can also be fought by getting the immune system to zero in on non-tumor antigens if these are coming from cells that, for some reason, help to support the tumor. Prostate cancer takes place in prostate cells, right? Well, all prostate cells – normal and abnormal – produce PSA (“prostate specific antigen”). If a vaccine successfully targeted PSA, a patient would wind up with no prostate cells, but by the same token no prostate cancer. Such a vaccine is under study now, at Duke among other places.

An approach quite similar to vaccination consists of developing a virus that will selectively infect only tumor cells. The immune system always seems to wake up for a virus and its way of eliminating the virus is to eliminate the infected cells. Bingo! There goes the cancer. A brain tumor infecting virus is currently in trials.

Cytokines: When we turn to cytokines and monoclonal antibodies, we are no longer trying to produce an educated immune system that will take over the cancer fighting job from then on. Rather we are taking mass-produced immune substances and processes and infusing them into the body. When these work, they either cause the immune system to do its thing or they take over from the immune system and accomplish the job. But once the infusions stop, the immunity stops. Of course if the cancer has been completely eliminated by then, this isn't a problem.

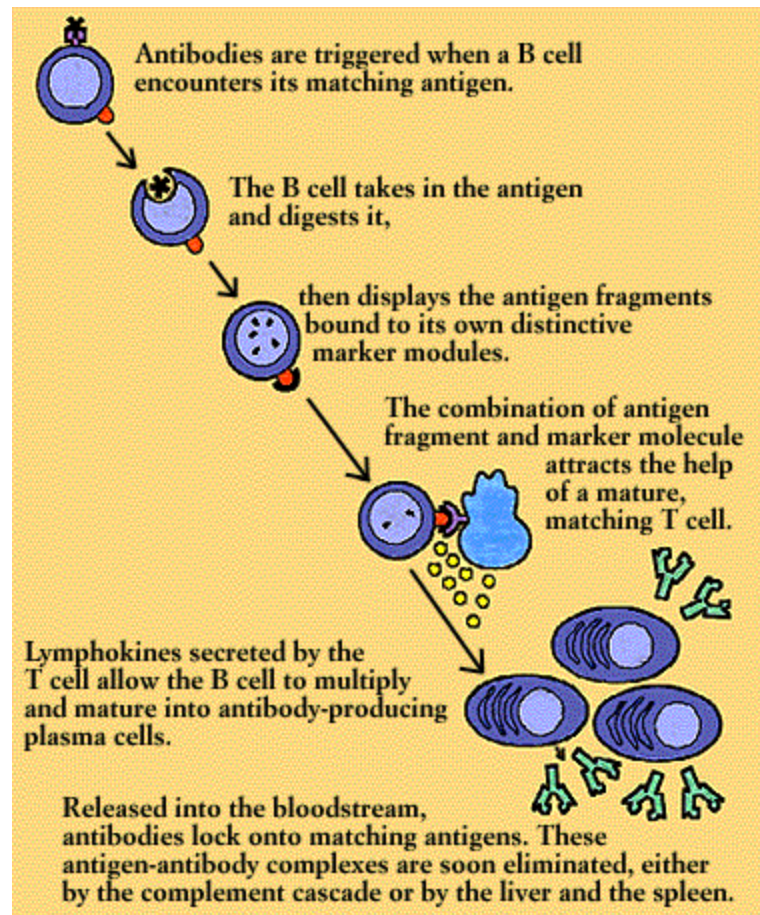
Cytokines are secreted by the cells of the immune system and act as messengers, in some cases increasing an immune response, in other cases dampening it. They have names like Interleukin -1, -2, -3 etc. or Interferon alpha, beta, etc. Others are given acronyms like TNF (“tumor necrosis factor”) or GM-CSF (“granulocyte macrophage colony stimulating factor”). These are the job applicants mentioned above that prefer to work in teams of their own choosing, but a couple at least have proved useful as single agent immune boosters. Interleukin-2 is the standard of care for non-operable kidney cancer. (Steve Dunn, whose Kidney Cancer and Clinical Trials web-pages we have praised in earlier newsletters, is a patient who achieved an enduring remission from high-dose Interleukin -2 and Interferon). Interleukin-2 also shows activity against melanoma. Interferon is highly active against melanoma and certain leukemias. GM-CSF has shown promise against melanoma; and Interleukin-12 is now generating some buzz among those studying it with mice.

Monoclonal antibodies: This is more like it. Here we not only find durable results in many cases, but a much more impressive rate of response. With monoclonal antibodies (MABs), we are essentially putting a robot immune system, programmed to do the job, in place of the natural immune system which has been falling down on the job. You've heard the names of many of these substances because

an exciting new one seems to debut about every nine months: Rituxan, Herceptin, Avastin, Erbitux, Gleevec, Zevalin, Oncolym... and the list in the pipeline is long. If your doctor proposes using something with "mab" or "nib" on the end of its generic name, she's proposing a monoclonal antibody.

MABs are biotech-designed, mass-produced antibodies targeted at something that either is the cancer or is supporting the cancer. MABs can be engineered to bind to either an antigen – the usual target of immune reactions - or a *growth factor receptor*, that is, a projection on the surface of a cell that takes in signals to stimulate the cell's growth and division. In the case of cancer, these growth signal receptors are often an excellent target for interference. The MAB need not even kill the cell harboring the receptor; it can simply occupy the receptor, thus preventing any growth factor signals from getting through.

When it comes to destroying cells, in the normal immune process, when an antibody locates its target on a cell, it binds to the cell and marks it for destruction. Other components of the immune system follow up to do the destructive work.



Part of the cascade of events triggered by an antigen

The man-made antibodies can step in and do the work of binding,

then recruit the normal immune system to do the destroying. Or the man-made antibodies can be supplied with their very own destructive toxins or radioactive molecules to deliver a killing dose to the target to which they bind. Or they can mark it for destruction by a drug that is infused later.

In a recently reported new investigative treatment, a MAB that carries with it nano-particles described as a "little golden shells" is infused into the body. A nano-particle can be as small as a molecule, and nanotechnology is a burgeoning field that promises to have immense implications for cancer treatment. The gold in our nano-MAB combination will take up heat if irradiated with "near infra-red radiation" (NIR), but living tissues remain cool. The MAB, with its attached golden shells, binds to the designated cancer cells and these cells die of over-heating when NIR is applied. The NIR passes completely harmlessly through the normal tissues of the body. This is my favorite pipeline method. Works great on mice. Still untested in humans.

Because they can locate the target throughout the body, non-lethal MABs can also be used for discovering cancer-related antigens throughout the body and thus diagnosing disease or monitoring its progress.

A short list of MAB treatments: Rituxan® (rituximab), the first MAB to be approved in this country, is effective against several forms of lymphoma. It uses the strategy of calling the immune system to the cells it has targeted, letting the immune system itself do the destructive work. Of late, a new pair of lymphoma-fighting MABs have appeared. Oncolym® (131I Lym-1 – in pipeline) and Zevalin® (ibritumomab tiuxetan) are both MABs with a radioactive substances attached that target proteins found only on the cancerous B cells in lymphoma. (It is ironical that cancers of the immune system, the lymphomas and leukemias, are the ones apparently most easily treated by the new robot immune processes).

Herceptin® (trastuzumab), which is effective in 20-30% of breast cancers, goes after and binds to cells that are expressing the Her2/neu growth factor receptor. In aggressive breast cancers, there are many tumor cells over-expressing this receptor and shutting them down crashes the tumor cell population.

Avastin® (bevacizumab) is the first anti-angiogenesis product to be approved. It is designed to work by inhibiting vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation, the process of angiogenesis. Shown to be effective against some colo-rectal cancers, and now in trials on other cancers.

Gleevec® (imatinib mesylate) is highly effective against chronic myelogenous leukemia and impressive as well against

gastro-intestinal stromal tumor (GIST). It shuts down a growth factor common to these cancers.

Erbitux® (cetuximab) binds to cells expressing Her1 receptors, another growth factor. It is effective against some colon cancers. Heard of Martha Stewart? Well, this is the drug whose producer's stock sale got Martha into legal trouble.

MabCampath® (alemtuzumab) binds to a molecule found on white blood cells. It is effective against chronic lymphocytic leukemia, producing complete remission in some cases.

There are some catches. MABs are not without their problems. Bodily processes other than the cancer can get side-swiped by MAB toxins or by the loss of growth factors. Long term use of Herceptin, for instance, eventually impacts the heart which apparently has some need for the Her2/neu that is being shut down. Zevalin impacts many normal as well as abnormal immune system cells, thus diminishing the patient's immune system; the patient may have to be followed up with transfusions for up to a year. There are also some tumors that MABs have trouble penetrating. Most problematic is the high cost of these treatments and the need to continue the infusions or pills, indefinitely in many cases, in order to keep the cancer at bay. But with the favorable response rates that can be obtained, and the sheer versatility of this approach, we can expect the trickle of MABs to swell to a virtual flood in the future.

A Note on Future Issues

Our "Cancer for Dummies" series is not finished. Indeed, lurking in the wings, there a new theory of how cancer works that is rather at odds with the prevailing view. We will try to explain it to you. But for now we need to take a break and discuss other, less technical, but quite crucial matters. Next month, we'll tackle an issue that's almost as scary as cancer itself - handling your expenses!

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