It has been standard advice that CLL patients should not receive vaccines containing live attenuated viruses. Thus MMR, oral polio, yellow fever and a few others are forbidden to patients with CLL, even those with mild disease.

The reasons for this are that patients with CLL have a profound immunodeficiency that is hard to measure. The most obvious manifestation is the low level of serum immunoglobulins, but there is also an ill-defined T-cell defect and a difficulty in antigen presentation by antigen presenting cells (APC).

Now all cancers are associated with poor immunity and all tumors of lymphocytes (lymphomas) have particularly poor immunity even among cancers, but CLL is worse than all the other lymphomas, with the possible exception of Hodgkin's disease. I think it is the APCs that are the main problem. These are necessary for foreign antigens to be processed into a form recognized by T-cells, and T-cells are necessary for B-cells to make antibody. Normally, dendritic cells are the APCs but in CLL the CLL cell can act as an APC – but a very poor one. I think that what is going on is that the CLL cells – being present to a numerically greater extent than dendritic cells – grab the available antigen and hide it from dendritic cells. Like dogs in the manger they can't do the job very well themselves but they don't allow the professionals to do the job properly.

The result is that response to vaccines in CLL is very poor. I demonstrated this along time ago (1974) using the bacteriophage phi-X-174. This is a virus that lives in the bacterium e. coli. It is a new antigen for humans, but very immunogenic. Patients with CLL are completely unable to make antibody to it when they see it for the first time, although if you keep injecting it about half will eventually make a smidgeon of a response. The interesting thing was that even stage A0 patients with very low white counts suffered from the same defect. Among our normal controls there was one individual who had a much better response than anyone else. Two years later he developed Hodgkin's disease – suggesting that even early Hodgkin's disease does not have the profound immunodeficiency that early CLL does.

Immunity to Herpes viruses is a special case. Most of us are exposed to most of the herpes viruses when we are children and we never get rid of them. The commonest example of this is a cold sore. If you've ever had one you're bound to have another. You know the things that bring them on: another virus infection like a cold, exposure to the sunlight, being run-down by any of life's troubles, chemotherapy – anything in fact that diminishes our immunity. This is because the herpes simplex virus, once it inside us stays there and is kept under control by the body's immune system. Herpes simplex II, which causes genital herpes, varicella/zoster, which causes chicken pox and shingles, EB virus, which causes glandular fever and CMV, which causes a variety of illnesses, are all herpes viruses that continue to live within us after an infection. CMV is especially interesting since about 15% of individuals over the age of 60 have never met it. It is a well known fact that untreated patients with CLL have increased numbers of T cells – but this is only true for those who have previously been infected with

CMV. It turns out that the excess T cells are programmed to keep the CMV under control. Similarly with EBV; a lot of T cells are keeping the EBV under control.

Varicella/zoster lives in nerve cells and if immunity drops it crawls out along the nerve the area of skin (a dermatome) supplied by that nerve and causes a very painful rash (shingles). This occurs in about a quarter of old people, but it is rather commoner than this in patients with CLL, and in CLL patients who are treated, especially with fludarabine of Campath, or who have a transplant, it is much more common, unless they have aciclovir prophylaxis. In those with the most severe immunodeficiency, the zoster rash will disseminate and become a florid chicken pox. What doesn't happen is patients with CLL catching shingles (or chicken pox for that matter) from a child with chicken pox. It seems that you can't get a superinfection with varicella/zoster, even if you are immunodeficient.

What has brought this up is some correspondence that doctor and CLL-sufferer, Brian Koffman, has been having with Dr Rafael Harpaz of the Herpes Virus Team, Division of Viral Diseases, NCIRD/CDC over the advice given by the Advisory Committee on Immunization Practices (ACIP) on vaccination against shingles in patients with CLL.

The statement that he and I both take exception to is "Patients with leukemia, lymphoma, or other malignancies whose disease is in remission and whose chemotherapy has been terminated for at least 3 months can receive live-virus vaccines."

As far as live viruses generally are concerned, this may well be true for solid tumors and for AML, CML and ALL, and perhaps for diffuse large B-cell lymphoma, but CLL is a special case among secondary immunodeficiencies since treatment makes the immunodeficiency worse, not better. The only treatments that induce complete remissions in any quantity are combinations containing purine analogues like fludarabine or the monoclonal antibody alemtuzumab. Both types of drug suppress CD4+ T-cells to AIDS-like levels and the suppression continues for at least six months in the case of alemtuzumab and in excess of two years in the case of fludarabine. We in the CLL community recommend that prophylaxis against pneumocystis continue for at least a year or until the CD4 count is greater than 200. It would be perverse to allow vaccination with live viruses at three months into a remission. The blood transfusion authorities insist on irradiated blood transfusions for patients who have received fludarabine or alemtuzumab, because of the risk of transfusion-induced graft versus host disease. I am sure that we should not allow treated CLL patients to receive live-virus vaccines.

In 30 years experience of treating CLL I have never known patients to recover their immunity, no matter what treatment has been given. Complete remissions in CLL are unsatisfactory, allowing the marrow to retain 30% lymphocytes. Newer standards of response involving elimination of minimal residual disease (MRD) have not been evaluated for any return of immunity, but suppression of

B-lymphocytes to this degree usually involves equivalent suppression of T-cells.

However, perhaps the zoster vaccine is a special case. This is how the ACIP argument runs:

"*Virtually all adults aged 60 and over are at risk of HZ (i.e., are infected with latent varicella zoster virus, or VZV). In contrast to other live vaccines, HZV does not protect by preventing infection but by preventing reactivation of this latent infection, which is much more likely in immunocompromised persons. A strategy of vaccinating household contacts would not protect a person with CLL (in contrast, say, to vaccinating household contacts with varicella vaccine to protect a child with leukemia).

* People receiving HZV have pre-existing immunity to VZV. While second episodes of chickenpox occasionally occur, second VZV infections remain uncommon even among the most profoundly immunocompromised persons and those rare episodes that do occur are not severe. Immunity to VZV in such patients appears to be adequate to protect against disseminated infection from the wild-type, natural VZV virus, and the risk of adverse effects from live-attenuated VZV contained in HZV should be correspondingly lower.

* In fact, there is empiric evidence to support the safety of HZV in immunocompromised persons. In early trials, the live-attenuated VZV used in varicella vaccine as well as HZV was administered to hundreds of profoundly immunocompromised children with leukemia in remission and *without* preexisting immunity to VZV, and the vaccine was well tolerated. These children tolerated subsequent second doses of the vaccine even better. Live attenuated VZV has since been safely and effectively used in many more children with other immunocompromising conditions such as transplant recipients and HIV infection. Live attenuated VZV is now recommended in HIV-infected persons without prior immunity to VZV. Finally, live attenuated VZV has also been used in HIV-infected children with prior varicella infection and immunity. As would be expected, the children tolerated the vaccination very well.

* General guidance on use of live attenuated vaccines by persons with leukemia has been evaluated by ACIP and published in their General Recommendations on Immunization published Dec. 2006 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm.) The document states that "Patients with leukemia, lymphoma, or other malignancies whose disease is in remission and whose chemotherapy has been terminated for at least 3 months can receive live-virus vaccines."

Given the potential severe, life threatening HZ in persons with CLL in remission, and the considerations regarding the safety of this vaccine, the ACIP recommends that the vaccine should be used in such circumstances."

Their argument is not without merit. It could well be that the presence of the

HZV virus under control signifies that there is sufficient protection against reinfection with new HZV and that an attenuated HZV virus vaccine would be without danger. I certainly hope so. But it would be foolhardy to accept this without an appropriate clinical trial. Experience in ALL in remission and among children with HIV infection before they become profoundly CD4+ T-lymphocytopenic is not relevant to what would happen in CLL.

A clinical trial is feasible, since it would be possible to vaccinate patients with antivirals standing by in case a serious infection ensues. I think that such a trial should be conducted, but it won't be as long as Merck is bolstered by the advice from ACIP.