take activated T cells to absorb out T cell growth factor, B cell growth factor remains in the medium. You could also absorb B cell growth factor with activated B cells," he continues. Results such as these also suggest that there are specific receptors for B cell growth factor just as there are for interleukin-2, the T cell growth factor. According to Paul, interleukin-2 elicits production by T cells of B cell growth factor and this may have been the source of the original confusion about whether interleukin-2 has B cell growth factor activity.

Although B cell growth factor and interleukin-1 stimulate proliferation of B cells, they are not sufficient to cause the cells to differentiate to the state in which they can produce antibody. Additional lymphokines, which are called B cell differentiation factors and secreted by T cells, are required for that.

There are indications, from Kishimoto's laboratory and that of Ellen Vitetta at the University of Texas Health Science Center in Dallas, among others, that the differentiation factors may be specific for the production of different antibody classes. For example, Vitetta's group has identified a factor that induces activated B cells to secrete antibodies of the immunoglobulin M (IgM) class and another factor that induces the secretion of an immunoglobulin G (IgG) molecule. These factors, Vitetta says, appear to work by increasing production of the messenger RNA's for the antibodies.

B cells normally produce an IgM first. As they differentiate to their final forms they may either continue producing an IgM or switch to any of the other four immunoglobulin classes. The Texas workers find the IgG does not appear until after the cells have been exposed to the appropriate differentiation factor. Before that they make an IgM and Vitetta hypothesizes that the factors may be involved in the immunoglobulin class switch.

In addition to the lymphokines that act on T and B cells, there are a variety of agents that act on macrophages, to attract them to regions where they are needed, to help hold them there, and also to cause their activation. Studies of these agents are not yet as advanced as those of the interleukins and the B cell growth and differentiation factors.

Immune recognition of foreign antigen is highly specific, but amplifying the response of a few cells to the point at which they can mount an effective immune attack clearly requires a complex interplay of nonspecific chemical signals for growth and differentiation.

—JEAN L. MARX

Promising Animal Model for MS

While the causative agent of multiple sclerosis remains illusive, the search continues for a useful model system that might yield some important clues to the human disease. One promising candidate, which involves visna virus, is being scrutinized by workers at the Johns Hopkins University School of Medicine, led by Janice Clements and Opendra Narayan.

The symptoms of the sheep disease include progressive muscular weakness, which is punctuated by periods of remission: paralysis and death often occur. The lesions in the brain are scattered, discrete loci of inflammation followed by demyelination. These patterns echo the human disease.

What especially intrigues Clements and her colleagues is the pulselike progression of visna infection, which presumably accounts for the alternating remission and relapse in the animal. Infected animals eventually mount an antibody response against the virus, but the subsequent emergence of a new antigenic variant produces a new round of infection. The animal and the virus are locked in a constant battle in which the pathogen repeatedly runs ahead of the host by the generation of new variants.

Although certain pathogenic parasites, such as schistosomes, deploy a large repertoire of antigenic variants in prolonged infections of their hosts, they do so by shuffling genes around their relatively large genomes. Visna, which is a 10-kilobase long, nononcogenic retrovirus, is not so generously equipped and must generate variants by more modest means. A number of pathogenic viruses show shifts in antigenic status, but few display the progressive antigenic variation in a single host seen in visna virus infection.

It turns out the emergence of new variants in visna is the outcome of an accumulation of point mutations in the 3′ region of the virus genome, a region that almost certainly codes for the coat glycoprotein. Until sequencing is complete in the parental strain and the subsequent variants it will not be possible to determine how many point mutations produce each variant nor precisely where the base changes occur. Visna is a relatively unknown retrovirus and so the Hopkins team faces an enormous amount of background work in these analyses.

One especially interesting aspect of the antigenic variation in visna is that the repertoire of variants produced in different hosts is very similar, though the order in which they appear may differ. Clements and her colleagues interpret this as a reflection of a limited number of regions on the glycoprotein molecule that are of biological significance. Presumably, other mutants either produce no change in antigenic characteristics of the molecule or induce a shift that is lethal in some way. The window for selection of variants is very narrow, says Clements.

Each new virus variant carries the accumulated mutations of its predecessors. New mutations, it seems, alter the antigenic profile of the virus coat just sufficiently for the organism to escape neutralization by existing antibodies. One result of this is that the antibody spectrum directed against the virus becomes progressively broader as the disease continues.

The mode of visna infection in sheep is unusual and underlies the pathological picture produced. The viruses infect monocytes, which are cells of the immune system that mature into macrophages. The brain lesions are caused, suggests Clements, when the immune cells invade the nerve tissue following some other primary infection. An inflammatory response arises as a result of the primary and possibly the secondary infection, and then subsides, leaving a small demyelinated area.

Between 60 and 70 percent of sheep in this country have antibodies to visna virus, but only a small proportion show any pathological signs of disease. The progressive weakness might be seen as a rare complication of a widespread infection, says Clements.

Whether multiple sclerosis fits this etiological profile is, at present, mere speculation. The Hopkins workers are, however, attracted by the notion of a neurotropic retrovirus as the causative agent in the human disease. At some point they will begin rigorously to test cross reactions between multiple sclerosis sera and visna and related viruses and to look for nucleic acid hybridization.—ROGER LEWIN