IMMUNOLOGY

# Antigens vs. antibodies

## Biologists and chemists take different roads toward an understanding of the mechanism that fights disease

by Christopher Weathersbee

An animal may be floored once by a germ such as the one that causes chicken pox, but on later contact take no notice at all. It has become immune.

Everyone knows it happens. What nobody really knows is how. If the immune response were fully understood it might be better controlled. Existing vaccines could be improved and new vaccines could be developed. Allergies and transplant rejection reactions, both immune response, might be conquered.

**The difficulty** in studying immune response is that the action takes place on the molecular level. There is no way to watch it happen. All a researcher can do is look at the aftermath and try to deduce what went on.

The same evidence can mean different things to different people. From the data available there have grown up two divergent theories of immune response, both zealously defended.

Any theory of immune response must explain two salient features of the process. The first is sensitization. Upon the first exposure to a germ or other antigen, several days may be required before an individual achieves peak production of antibodies.

On subsequent exposure, however, the body appears to remember the first trial and is ready to produce the appropriate antibody. This secondary response is fast and massive, often peaking within a few hours.

**Also** in need of explanation is the extraordinary specificity of the immune reaction. All data so far obtained support the idea that each antibody is good for only one antigen and each antigen stimulates the production of only one antibody. The body may remember exposure to one flu virus yet be unprepared for the virus' first cousin.

One of the two basic theories of immunity takes the chemical approach, the other a more biological approach. The chemical theory, called the template theory, received much attention two or three years ago, with much of the work being done in England. The biological or clonal theory, sometimes also called the selective theory, recently has achieved some ascendency, possibly because of the increasing work being done in genetics.

The two leading proponents of the template theory are physical chemist Linus Pauling of the University of California and protein chemist Felix Haurowitz of the University of Indiana. They theorize that an antigen, be it virus, bacterium, poorly matched blood cell, organic chemical toxin, or whatever foreign macromolecule, makes its way into the bloodstream and encounters a form of white blood cell called a leukocyte which absorbs it.

Like all nuclei, the nucleus of the leukocyte contains strands of deoxyribonucleic acid (DNA) bearing genes. In the normal operation of the nucleus certain of these genes are inactive. Certain others serve as templates for the building of molecules of messenger ribonucleic acid (mRNA). The mRNA migrates out of the nucleus into the cytoplasm of the cell, where it attaches itself to a kind of cellular workbench called a ribosome. There it serves in its turn as a template for the construction of protein molecules. Each gene makes a specific form of mRNA, and each mRNA makes a specific protein. In this way the function of the cell and ultimately of the whole organism is controlled by the gene.

**The chemists** hold that the antigen particle absorbed by the leukocyte somehow takes the place of the mRNA produced by the genes. The antigen serves as the specific mold for its own antibodies, which pass into the bloodstream to combine with and neutralize any antigen still at large.

Later modifications of the theory postulate an essential role for large amoeba-like cells called macrophages. These engulf the antigen particles, break them into fragments, and pass the fragments on to leukocytes. Leukocytes have been shown in time-lapse microphotographs to crowd around macrophages. The larger cells appear to form tubular connections with the leukocytes, and material is seen flowing from macrophage to leukocyte.

The biologists declare that the theory jibes not at all with modern concepts of genetic action. Antibodies are proteins and all protein patterns, they say, must be read off DNA by mRNA. How can an antigen usurp the role of both gene and mRNA without raising the possibility of cellular anarchy? And by what mechanism is secondary response achieved under the template theory?

An answer to both these questions has been suggested by Dr. Brigitte Askonas of the National Institute for Medical Research in London and more or less independently by a team at California Institute of Technology under Dr. Justine Garvey. These workers noticed that antigen fragments, by themselves often not antigenic, can be found in the body joined to a form of RNA. Tiny amounts of these complexes persist, apparently indefinitely.

The hypothesis is that the macrophage synthesizes the RNA and combines it with the antigen fragments before passing the complex to the leukocytes. The leukocytes behave as if the RNA-antigen molecule were its own mRNA. After the primary response is over, small amounts of the complex are stored, possibly in the liver. Another exposure to the same antigen releases these molecules, which then act as super antigens, stimulating the faster, more massive secondary response.

The biologists are far from satisfied. They still smell heresy: interference with the role of the gene.

Sir F. M. Burnet of the Hall Institute in Melbourne, Australia, and Sir Peter Medawar of the NIMR in London won a biology and medicine Nobel Prize in 1960 for developing the alternative clonal theory. Dr. Joshua Lederberg of Stanford University is among its leading American proponents.

The clonal theory rests on the belief that the bloodstream contains a vast variety of leukocytes. For every possible antigen there is a small group of leukocytes bearing the necessary active genes for the production of an appropriate antibody.

An incoming antigen floats in the bloodstream until it runs across one of these appropriate leukocytes. The meeting stimulates intensive cell division by the leukocyte until a group, or clone, of daughter cells is formed; it proceeds to grind out the needed antibody.

A residue of the daughter cells remains after primary response. This residue makes subsequent recognition of the antigen more likely, thus faster.

This theory meets the requirements of genetics. The DNA is indeed the source of the antibody's design. The clonal theory in fact has held the inside track for a while because of its agreement with genetics. But it faces its own contradiction, and a large one. There are millions of naturally occurring proteins which could be antigenic to a given organism. There are millions more synthetic antigens possible, and some already have been proved able to induce immune response. How can an organism afford to be ready for all of them?

Genetic capacity is after all finite, even if vast. With all the great and small machinery of the body to control, how can so much of this capacity be given over to defenses with an extremely low likelihood of ever being used?

There has got to be a better explanation than either theory. The best answer may well lie between the two.