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COVER A human eosinophil (upper right) is adhering to the surface of a larval schistosome that was coated with antibodies from patients suffering from schistosomiasis. The cell membrane is broken and granules are spilling from the cell (×11,000). See page 1065. [Courtesy of John P. Caulfield, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115]

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Frontiers in Immunology

It could be said that immunology is both the most ancient and the most modern of sciences, the most theoretical and the most practical. The basic concept of immunology was mentioned by Thucydides writing during the time of the Peloponnesian Wars. He noted that the sick could be treated by those who had recovered since they were free of fear. The idea that survivors of infection were immune to a second infection thus appeared long ago. Edward Jenner's perception in regard to milk maids' smooth complexions—that is, with faces unscarred by smallpox—led to the idea that vaccination with cowpox might protect against smallpox. Louis Pasteur built on this concept of an attenuated virus to start the era of ever more extensive vaccination and immunities in the world today. But this highly effective approach to public health has in turn led to a theoretical framework that has extended beyond immunology into the understanding of differentiation, gene expression, and protein structure. Bennett and Dreyer's postulation and Tonegawa's demonstration of "two genes–one polypeptide chain" launched a study of DNA relationships to the antibody structure that has extended insights far beyond the field of immunology itself.

In this issue of *Science*, some of the forefronts in this prolific area are described. One of the incredible puzzles is the ability of the immune system to make a specific response to an almost infinite spectrum of man-made and natural molecules and to distinguish protein molecules made by self from almost identical proteins from non-self. The newest insights into the mechanism for producing the preimmune repertoire of approximately 10^7 different antibody molecules in B cells are described by Alt, Blackwell, and Yankopoulos, who focus mainly on the diversity generated by joinings of gene segments that make up the variable region of B cell antibodies. The subsequent expansion of particular B cell clones during an immune response and the generation of new variable regions by somatic hypermutations are the subjects treated by Rajewsky, Förster, and Cumano. The other half of the immune system, the T cell, uses many of the joining mechanisms of B cells but has the added need to recognize the major histocompatibility complex. How this system creates the additional capacity for distinguishing between self and non-self is an intriguing problem that is discussed by Marrack and Kappler.

These advances in knowledge do not preclude surprises. In the early history of immunology, the bursas of chickens were found to be a source of antibody diversity and the human analog, bone marrow, was deduced to be similar. Imagine the consternation created by the finding that chickens use an entirely different mechanism for diversity, one involving gene conversion instead of gene rearrangement. That subject, explored by Weill and Reynaud, provides a cautionary flag in regard to too easy generalization from one to all species.

Immunology has been a field in which practical application has been ahead and has led to theoretical understanding, and two other articles illustrate this fact. Vitetta *et al.* describe a flourishing field in which a biological guided missile, an immunotoxin, is created by combining an antibody to a tumor cell and a cellular toxin in order to specifically kill tumor cells. The application of immune techniques, described by Capron *et al.*, to the cure of schistosomiasis, a debilitating parasitic disease affecting 200 million people, reveals that parasites have developed incredible stealth systems to evade the immune apparatus of higher vertebrates. Vaccines against such parasites still remain one of the most difficult goals of modern immunology, and understanding the fundamental mechanism is going to be essential for the development of successful vaccines.

The importance of the immune system is indicated by the fact that the number of cells in our bodies devoted to the immune system is approximately equal to the number of cells in the brain. Only a few years ago, immunologists elicited derision from "hard scientists" by defining an antibody as "a molecule generated by an antigen" and an antigen as "a molecule which reacts with an antibody." That seemingly circuitous reasoning has revealed the most sophisticated molecular and practical applications of any biological system. This field has mysteries still unsolved but it is one in which every step along the path produces some benefit to mankind.—D. E. KOSHLAND, JR.