Comments and Communications

Immunologic

"Immunology" refers to a study of immunity or resistance to infection. The word "immunity" implies nothing with regard to any specific mechanism whereby it operates.

Immunity is a concept, implying that various constitutional factors may lead to an unusual resistance to infection. The one thing implied about the nature of these factors is that they are constitutional. The absence of mosquitoes or the death of bacteria may lead to what appears to be immunity, but it is not. Some factors which lead to a greater than normal resistance must reside in the exposed person.

Another word commonly used in bacteriology is "serology." This refers basically to the study of any reactions in which the serum of the blood is a component, but it is proper and helpful to restrict it to the study of reactions between proteins, called antigens, and certain globulins, called antibodies, found in the serum of the blood of animals inoculated with these proteins. Serology deals with specific observable reactions; in this sense it is observational rather than conceptual. The word "serology" implies nothing as to biologic connotations.

Let us now turn to a chapter on "immunology" in any textbook. In the first paragraphs we get an idea of the concept that resistance to infection varies; hence, there may be, relatively, the extremes, susceptibility and immunity. The gradient is given a fictitious solidity by bounding it with rigid definitions incompatible with so broad a concept, but it is there. There is an apologetic note; philosophic ideas are unworthy of mention in serious science because they cannot be weighed.

The chapter then shifts, frankly or subtly, to a discussion of what it calls the mechanism of immunity. This is introduced by a discussion of antigens and antibodies in which we learn that complex proteins, or antigens, when injected into animals, stimulate the formation of antibodies. When properly mixed, antigens and antibodies produce some demonstrable reactions.

In connecting the concept of immunity and the facts of serology, the text encounters semantic difficulties. It talks about "defensive mechanisms" and "protective" antibodies. Animals are "immunized." Cautious writers let readers catch themselves in these traps; less cautious writers say flatly that the mechanism of immunity depends on antibodies. Readers are told or led to believe that serology is a study of the mechanism of immunity. If asked, most authors would admit readily that cellular, mechanical, chemical, and other factors contribute to immunity. The reader of the text cannot ask them and does not get this impression.

Here is our argument. The concept of immunity does not imply any specific mechanisms. They are unquestionably complex. They need not be alike in two different diseases. Serology, a study of observed reactions between antigens and antibodies, implies nothing intrinsically connected with immunity.

Possible relationships between immunity and serologic reactions constitute a *third* step in argument. Both the thoughts and the science behind immunology and behind serology are initially distinct. If we postulate as a third step that immunity is only an expression or a consequence of serologic reactions, we find more exceptions than agreements, but that need not concern us here. The point is only that the concept of immunity and the observations of serology should always be considered separately. Any move to bring them together should be deliberate and specific for specific situations. The causal connection is not general. Experts properly may argue about the relationships in any specific case. They cannot properly argue about either the immunologic concept or the serologic facts. Both the solidity of argument and clarity of understanding are improved by definite separation of these two ideas. Separation can be accepted equally by ardent believers in serologic explanations of immunity and by those who have other theories for explanation.

Once the divorce is effected, the semantics offers no trouble. We may *inoculate* an animal rather than "immunize" it. To newcomers, the thought of "immunizing" a rabbit is puzzling. How can you "immunize" a rabbit by inoculating it with a harmless substance, say the white of an egg or the dead bacilli of typhoid fever, to which in the living form the animal is resistant? When we collect serum from the blood of this rabbit, surely we may better call it an *antiserum* than an "immune serum." Andrews, in his recent *History of scientific English*, objects to "immunopolysaccharide" because it comes, a bit pompously, from three languages. We add oil to his good fire. The word is serologic; it refers to a form of antigen. Whether or not it has to do with immunity is open to debate with each substance to which these 8 syllables may be applied. Often, at least, there is no connection.

The phrase "immune serum" is startling to newcomers. How can a serum be immune or susceptible? Even if the serum could produce an immunity, usually not to the point, the serum is not immune. The phrase refers only to sera which contain antibodies. No immunologic thought is even possible with most of these sera. The word *antiserum* covers every thought involved without complicating the semantics; it does not imply too much, it inhibits no one's thoughts, it adds no new word or new connotation.

The semantic confusion of immunologic and serologic ideas distorts the thinking of students and their teachers and inhibits the development of our knowledge. Simple serologic explanations of immunity have caught the fancy of bacteriologists who should know better and consequently are accepted by those who depend on bacteriologists for their bacteriology. For 50 years, whenever the cause of a disease has been discovered, an immunizing vaccine and a therapeutic serum are immediately prophe-

sied because, by serologic theory, immunity is simple. The idea has an anthropocentric or teleologic appeal. It satisfies our curiosities. We like to think that everything is designed for our own good. Investigators work on serologic problems, report serologic observations, and then draw immunologic conclusions. Serology is laboratory stuff, but immunology is Big Time. Experts, on whom we must rely for authoritative information, have an obligation. Bacteriologists have rested their conclusions on a misleading argument for so long that they fool even themselves and each other.

The simple thought that antigens and antibodies explain immunity leads to serious errors with vaccines and therapeutic antisera. The persistence of searches for good vaccines is a tribute to human optimism. The persistence of the sophistry that anything which stimulates the production of antibodies is a vaccine is remarkable, but it is no tribute. The introduction of an antigen into an animal necessarily, by definition, stimulates the production of antibodies. The literature is full of writers who, after introducing evident antigens, express surprise over the discovery of antibodies. To argue that a vaccine produces a resistance to infection because it has stimulated the production of antibodies confounds theory, speculation, and fact. It would be equally logical to account for the immunity by the sore arm produced and to vaccinate with a club. Thousands of purported vaccines have failed immunologically; all stimulated the production of antibodies. No vaccine could fail if we accept the fallacious confusion of immunology and serology. Vaccines do fail, often, immunologically.

Although the serum of any animal which has been inoculated with antigen must contain antibodies, the antiserum may have no immunologic value. There is often no possible relation to immunity. Are we to suppose that the inoculation of a person with the organisms which cause fire blight of pear trees would be an immunizing process? There would be antibodies.

Here is a specific example. Typhoid vaccine, one of the few successful vaccines, confers a significant resistance. Those who are vaccinated rarely have typhoid fever after ordinary exposure. This is demonstrated by the rates of infection in vaccinated and in unvaccinated persons in regions in which the disease is common. An attack of typhoid fever also confers an adequate immunity in those who recover. There is exposure to the antigenic components of the bacillus of typhoid fever with either infection or vaccination. Therefore, antibodies are formed. Should we yield to the temptation to argue that the immunity is *caused* by the antibodies? The factual observation is *only* that in this case antibodies and immunity usually coincide. But apparently serum of high antibody content is not of immunizing value, and quite surely persons with very little antibody after vaccination are as immune as those with much. We may also argue that in any infection permitting absorption of antigen there are antibodies, but in only a few do we have immunity or vaccines. That immunity and antibodies coincide proves nothing about causal relationship. Other explanations of the immunity have a stronger claim.

We are reporting an experiment. These ideas have been tried consistently on many academic and professional students. It is no trouble to lecture without mixing serology and immunology. It antagonizes no one, and it disturbs no one's right to decide when he wishes to relate immunity and serology. None of us working with our classes uses the inappropriate terms, such as "immunizing" a rabbit; each catches these phrases when others use them. There is no dogma in this. The dogma is in the enforced relationship between immunity and serology, not in the freedom which we should like to promote.

The origin of the confusion does not excuse it. The reactions between toxins, which are also antigens, and their antibodies happen to result in the neutralization of the poisonous properties of the toxins. This early observation, antedating other serologic observations, combines an immunologic concept and a serologic observation. Serologic principles arose from this observation and phenomena observed later. Introduce the white of an egg into a rabbit and there is stimulated the formation of antibodies which will precipitate the white of an egg. There is no immunologic thought whatever in this. Serology has expanded to a useful and moderately exact branch of science. It is incumbent upon us to keep it separate from immunity except when the connection is clear and irrefutable. Only after immunologic thoughts and serologic facts are each separately understood can possible relationships be examined. *First,* there is the immunologic concept concerned. *Second,* there are the observed serologic phenomena. *Third,* there may be considered combinations. Occasionally, and not often, immunologic phenomena appear to have serologic mechanisms.

We plead for separation of the concept of immunity and the phenomena of serology. Separation leads to a more precise expression of facts and arguments and to fewer fallacious deductions from our observations. Separation can be done with language, but so deeply is the error planted that bacteriologists can get out of it only by prolonged effort. We owe this effort to students and to others who wish to grasp something of scientific thought. We owe it to science, built upon reliance in the observations and logic of specialists in each component of science.

M. S. MARSHALL

Division of Bacteriology,
University of California Medical School, San Francisco

A Comparison of the Total Leucocyte Count in the Heart Blood and Peripheral Blood of the Rat

In a recent issue of *Science* (April 30, p. 447) Quimby, Saxon, and Goff reported that the leucocyte count of the heart blood in the rat is only about one-fourth that of the peripheral blood (heart blood = 6,425 leucocytes/mm^3; tail blood = 23,810). In view of the large number of experiments which have been based on leucocyte counts of tail blood, this report seemed worth checking.