Making antibodies act like enzymes

By adding the catalytic virtues of enzymes to the binding abilities of antibodies, two teams of scientists say they have made the first catalytic antibodies. They say their work illustrates a powerful new strategy for designing specialized molecular tools for research in biology, chemical synthesis and medicine. Specific biomedical applications could someday include dissolving blood clots and cutting up viruses, they suggest.

Molecular biologists Alfonso Tramontano, Kim D. Janda and Richard A. Lerner of the Scripps Clinic and Research Foundation in La Jolla, Calif., and chemists Scott J. Pollack, Jeffrey W. Jacobs and Peter G. Schultz of the University of California at Berkeley performed the separate studies, described in the Dec. 19 SCIENCE. "This is the first real demonstration of catalytic antibodies," says Schultz.

Antibodies are nature's masters at recognizing and binding to specific molecular structures. Their biological responsibility is to advertise the presence of foreign, and often infectious, antigens in the blood and tissues so that antigen-eating macrophages or other complex immune mechanisms know where to go. Biological catalysts or enzymes are nature's experts at negotiating the occurrence of specific chemical reactions within organisms. Without enzymes, many of these vital reactions would require temperatures or pH conditions that organisms cannot withstand.

Stanford University emeritus chemistry professor Linus Pauling suggested in 1948 that enzymes might be able to do such things by strongly binding to the reacting molecules, or substrates, in ways that favor midreaction "transition state" structures, which then quickly rearrange into the products of the reaction. Any factor that favors these transition states over other possible structures would increase the rate of the reaction.

The Scripps scientists reasoned that if Pauling's conjecture is correct, they might be able to make a chemical receptor, such as an antibody, that binds specifically to molecules that "look" like the theoretical transition states of an enzyme's specific substrate. "Then you could use that binding energy to do chemical work," Lerner says. According to this line of thought, appropriate antibodies might bind the actual substrate in such a way that they catalyze reactions normally executed by enzymes.

The Scripps group synthesized compounds called phosphonate esters, which resemble the biologically vital structures called carboxylic esters in their transition states as they undergo cleavage by water, or hydrolysis. The scientists injected the phosphonate esters into mice to elicit antibodies, which they hoped would not only bind to specific carboxylic esters but also enzymatically cleave or hydrolyze specific chemical bonds. After purifying and cloning the antibodies, the scientists found that they do hydrolyze carboxylic esters, but only if the esters have been chemically "activated," or destabilized, beforehand.

"We'd like to develop antibodies that catalyze substrates that don't require prior activation," says chemist E.T. Kaiser at Rockefeller University in New York City. "But it's really a good beginning to the whole problem of trying to develop catalytic antibodies."

The Berkeley trio used another tactic. They identified existing antibodies that bind specifically to a compound that closely resembles the transition state of carbonate compounds, which also contain ester structures. Here, too, the antibodies bound only to molecules closely related to those compounds for which the antibodies were chosen, and the antibodies catalyzed hydrolysis reactions in the manner of enzymes.

"Lerner's work and my work show that it can be done and that the idea of catalytic antibodies is viable," says Schultz. "But to really do it right and extend it to other systems you have to know how and why it's working."

So far the two groups have succeeded in designing catalytic antibodies that perform one kind of reaction. But Lerner says he will be able to design enzymatic antibodies, or "abzymes," that perform a range of chemical jobs such as making and breaking specific bonds between the amino acids that make up proteins. "We're looking at a huge variety of reactions," says Shultz.

Lerner says this work could usher in a "new era" of discovering finer details about how enzymes work. The researchers say their work could lead to ways of obtaining enzymes tailor-made for just about any purpose a molecular biologist could dream up. —*I. Amato*

Do you hear what I hear?

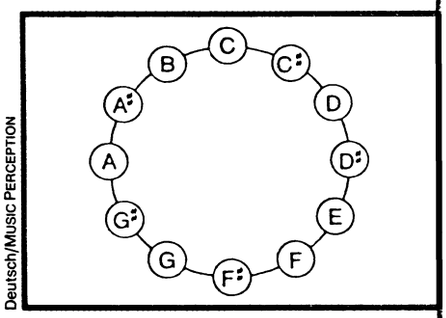
Music critics have been known to disagree violently about the merits of a piece of music. Part of the reason may lie in the recent discovery that what one person hears can be strikingly different from what another hears. Some aspects of music appear to reside in the mind of the listener.

The discovery, made by psychologist Diana Deutsch of the University of California at San Diego, concerns pairs of tones that are a half octave apart. When one tone of a pair, followed by a second, is played, some listeners hear the second tone as higher in pitch than the first. Other people, hearing the same tones, insist that the second tone appears to be lower in pitch.

Furthermore, when the pattern is recorded on tape and then played back at different speeds, it can be heard as either ascending or descending, depending on the playback speed. A listener who hears the pattern as ascending at one speed may very well hear the pair of tones as descending at another speed. In visual terms, this musical effect is as paradoxical as seeing a square instead of a circle when the shape is shifted to a different location.

"It's a very unexpected finding," says Deutsch, "and it's a great surprise to people." For any one individual, a given pattern will clearly and consistently sound either ascending or descending. That person's neighbors, however, could be hearing exactly the opposite. Deutsch demonstrated the effect at last week's Acoustical Society of America meeting in Anaheim, Calif.

Each tone used in Deutsch's experiments is constructed from a set of sinusoidal waves that makes it easy to identify whether a tone is, for example, the musical note C but not whether it happens to be a high or low C. The resulting tones sound a lot like notes that would come out of an organ. The experiments don't work on, say, a piano keyboard, because each piano note has a more complex structure than the experimental tones, and listeners apparently use those extra clues to determine relative pitch.



Deutsch/MUSIC PERCEPTION

Deutsch's experiments seem to indicate that most people carry around a "pitch-class circle" (see diagram) in their minds. Tones in one region of the circle are generally heard as higher, and tones in the opposite region as lower. The orientation of that circle, however, appears to vary from person to person.

"It raises the very important issue of how much commonality there really is among people when listening to music," says Deutsch. "It's certainly possible that people listening to certain orchestral pieces are going to hear them in ways that are different from each other and be unaware of that."

—*I. Peterson*