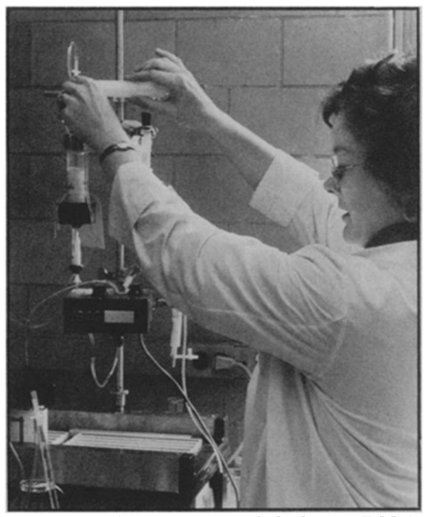
The Intrigue of Antibody Genetics

The constant region of each antibody chain is coded by a handful of genes. How about the variable region?

by Joan Arehart-Treichel

Leder: "Unique protein molecules."



Nau purifies immunoglobulin mRNA.

During the past decade, enormous progress has been made in unraveling one of the great mysteries of the human body—the chemistry of the million or so antibodies that are able to combine with as many different antigens. "Antibodies," declares Donald D. Brown of the Carnegie Institution of Washington, "are one of the detective stories of modern biology."

It is now known that there are five different classes of antibodies (immunoglobulins). The basic structure of each class consists of groups of two protein subunits—one a lightweight polypeptide chain and one a heavy polypeptide chain. Each chain contains a so-called constant region and a so-called variable region. While the constant regions of chains are identical from one antibody to another, the variable regions differ.

It is this difference in variable regions that gives antibodies their antigenic specificity. It is what lets them recognize one of the million or so antigens capable of attacking the body during a lifetime and of combining with that antigen and destroying it.

Antibodies are made by cells that derive from bone marrow and end up in the spleen, lymph nodes, appendix and other lymphoid tissues. These cells are called B lymphocytes. Each lymphocyte makes an antibody that is specific to a single antigen. That raises a provocative question about the genetics of antibodies. How many genes does each lymphocyte use to code for each antibody chain it makes?

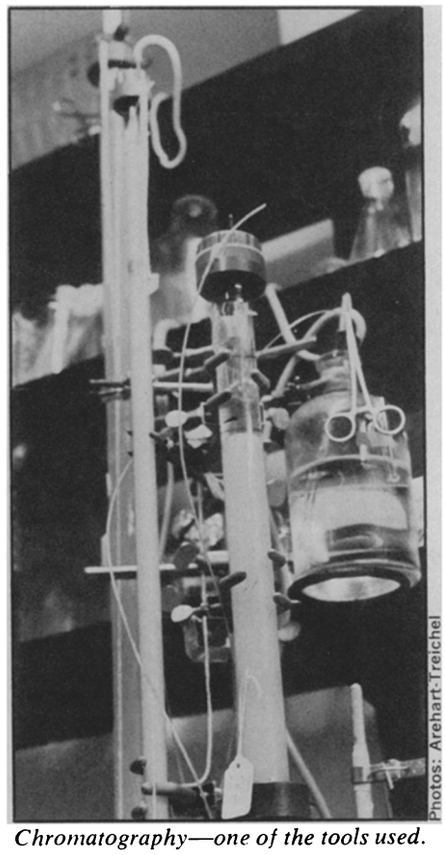
Ample evidence now suggests that the constant region of an antibody chain and the variable region of the same chain are coded by different genes. This evidence contradicts the biological dogma that one gene codes for one polypeptide chain. So it appears, as Philip Leder of the National Institute of Child Health and Human Development points out, "that antibodies are made in a strange way and are unique protein molecules."

But if two genes at least are involved in making an antibody chain, another perplexing question needs to be answered. Does a lymphocyte contain only one gene that codes for the constant region of an antibody chain, and only one gene that codes for the variable region of the chain? Or might more genes be involved? Although the number of genes coding for the variable region is not yet known, American and Swiss research indicates that the constant region is encoded by one, or at most, by a handful of genes.

C. H. Faust, H. Diggelmann and B. Mach of the University of Geneva and of the Swiss Institute for Experimental Cancer Research in Lausanne reported in the June PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES that from one to five genes are involved in coding for the constant region of an antibody chain. Leder, along with his colleagues Tasku Honjo, Symour Packman, David Swan, Marian Nau and Barbara Norman, reported in the September PROCEEDINGS that three genes appear to be involved in coding for the constant region of an antibody chain.

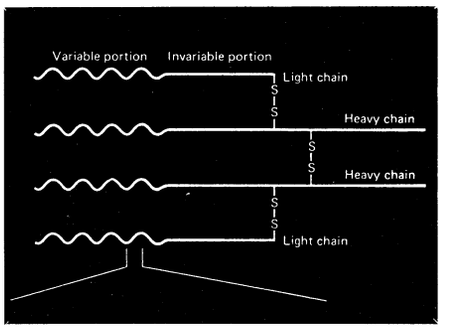
In other words, anywhere from one to five genes—probably three—in one B lymphocyte code for the constant region of each polypeptide chain that helps make up an antibody.

Both groups of immunogeneticists used similar procedures. They took a lightweight chain from an immunoglobulin of a mouse myeloma tumor. They used this kind of immunoglobulin because it is easily available and its chemistry is identical to that of antibodies. After obtaining the light chain, they used affinity chromatography and centrifugation to obtain a relatively pure messenger RNA molecule corresponding to it. They took the reverse transcriptase enzyme, which is able to make DNA copies of RNA molecules, and made a DNA copy of the



Photos: Arehart-Treichel

Chromatography—one of the tools used.



The basic structure of an antibody.

messenger RNA that corresponded only to the constant region of the light chain —not to its variable region.

They hybridized (crossed) the DNA copy of the constant region of the light chain with DNA taken from a mouse myeloma tumor cell. These results showed, in the instance of the Swiss experiments, that the DNA copy and the cellular DNA stuck together in one to five different places. In the American experiments, the DNA matched in three places. These results can be interpreted to mean that each place where cellular DNA stuck to DNA corresponding to the constant region of the light chain, the genetic material was identical. In other words, these stretches of DNA are the genes that code for the constant region of the immunoglobulin light chain. Presumably the same number of genes is involved in coding for the constant regions of all chains that make up antibodies.

So each B lymphocyte uses anywhere from one to five genes (probably three) to make the constant region of each polypeptide chain that helps make up an antibody. But how about the number of genes that code for the variable region of each chain? Until more evidence is obtained, there are some tantalizing possibilities. For instance: Since variable regions are identical in one particular antibody, but differ from one kind of antibody to another, do all B lymphocytes possess the same genes that code for the constant regions of antibodies, yet differ in the genes that code for variable (antigen-specific) regions? Or do all B lymphocytes contain the same genes, but only activate those needed for specific variable regions? This would mean that each lymphocyte needs some three genes to code for the constant region of each antibody chain, but would contain some million genes having the potential to code for the variable regions of antibody chains. This would be a formidable number per B cell.

All sorts of possible combinations between constant and variable genes are now being explored by immunogeneticists. They are also trying to determine how antibody chain regions coded by different genes are linked up into one polypeptide chain. □