also enhance the growth of tumors of the corresponding type that have been transplanted into animals.

Additional evidence for the importance of blocking factors in cancer etiology has been obtained by the Hellströms. They found that patients with primary melanoma that had not metastasized no longer had blocking activity in their serum after their tumors were removed surgically. Patients with progressive metastatic melanoma did have the activity. Finally, in patients who had been in remission from the disease and subsequently relapsed, blocking factor reappeared in the serum 2 to 6 months before their relapses were clinically detectable. Although these and other studies indicate that blocking factors may play a role in promoting or permitting tumor growth in vivo, the case has not yet been definitively proved. At the very least, however, knowledge of an individual's blocking factor status may be of diagnostic or prognostic value.

The biochemical nature of blocking factor is still uncertain. The Hellströms originally thought that it was antibody against tumor antigens. Such antibody could block by binding to antigen on tumor cell membranes and preventing attack by sensitized lymphocytes. If this were true, stimulation of the immune system as an immunotherapeutic strategy could do more harm than good if humoral immunity—and thus the production of blocking antibody—were stimulated in addition to cell-mediated immunity.

More recent evidence supports the hypothesis that blocking factor is either a complex of antibody with tumor antigen or is tumor antigen itself. The Hellströms, with Sjögren and Bansal, found that they could separate blocking factor into two fractions. One contained components, including antibodies, with molecular weights greater than 100,000; the other contained substances with lower molecular weights and included antigens. Under the standard conditions employed by the Hellströms for their in vitro assay system (incubation of cultured tumor cells with the material to be tested for blocking activity and removal of that material before addition of lymphocytes), both fractions were required for blocking activity. Antigen alone prevented the cytotoxic effects of lymphocytes but only when it remained with the lymphocytes throughout the entire test. Antigen may act directly on the lymphocytes rather than on the tumor cells.

Robert Baldwin and his associates at the University of Nottingham, England, have additional evidence that complexes of tumor antigens with antibody cause blocking. They isolated tumor-associated antigens from hepatoma cells. (A hepatoma is a liver tumor.) Serum taken from rats following surgical removal of their hepatomas contains antibody against tumor antigens but it does not block the cytotoxic effect of lymphocytes on cultured hepatoma cells. Baldwin and his colleagues could restore blocking activity by adding isolated antigen to the serum. Blocking occurred only when the proper ratio of antigen to antibody was attained. Addition of either too

Lithium Primary Cells: Serendipitous Search

Another piece of evidence in the ongoing debate between those who advocate that scientific research be directed toward solving specific practical problems and those who believe that practical benefits can flow from undirected research has been contributed over the last 2 years in the form of the discovery of a new primary cell (battery) based on lithium and liquid chlorine compounds by scientists at the GTE Laboratories, Waltham, Massachusetts (*1*), and by researchers at the Army Electronics Command, Fort Monmouth, New Jersey (*2*).

Primary cells, as distinguished from the secondary cells which make up storage batteries, cannot be recharged, but still find wide application as power supplies for items as mundane as flashlights and transistor radios and as sophisticated as heart pacemakers and aerospace electronics.

The name of the game in battery research is to find an electrochemical system that can be made to deliver a high specific energy, usually expressed in watt-hours per kilogram (1 watt-hour = 3600 joules), in a small volume. Not infrequently, the batteries in a piece of electronic equipment take up the largest part of its volume. For some applications requiring a rapid battery discharge, a high specific power (watts per kilogram) is desirable. A long shelf life (the time the battery sits unused) is also needed. But most importantly, the whole package must be inexpensive.

For years, battery researchers have been fascinated with the prospect of using lithium as the anode material in batteries, because of its light weight and extremely electropositive character. Because of the reactivity of lithium with water, however, most such cells have required (for room temperature operation) an organic solvent to contain the electrolyte, or molten salt electrolytes which operate at high temperatures. In recent years, for example, a room temperature lithium primary cell has been developed which uses sulfur dioxide (SO_2) dissolved in an organic solvent (along with a lithium halide electrolyte) as the active cathode reactant. The sulfur dioxide cells, now manufactured by at least two battery companies, demonstrated the principle that the soluble cathode reactant can contact the lithium in the cell without reacting with it. Instead, a passivating layer of reaction products inhibits the reaction.

The new primary cell under development by GTE Laboratories and the Army differs from the sulfur dioxide cell in that the cathode reactant [liquid oxyhalides, such as thionyl chloride ($SOCl_2$) or sulfuryl chloride (SO_2Cl_2)] also serves as the sole solvent for the electrolyte [usually lithium tetrachloroaluminate ($LiAlCl_4$)]. As in the sulfur dioxide cell, a low weight, high surface area carbon positive electrode acts as a catalyst for the reduction of the cathode reactants, thus permitting the cell reaction to proceed. Since the solvent acts as the "fuel" for the cell, there is no need for a separate supply of cathode reactants, and the attendant result is a greatly reduced cell weight and increased specific energy.

Curiously enough, the GTE scientists did not start by

little or too much antigen to the serum produced no blocking activity. Baldwin thinks that large complexes of antibody with antigen, which can bind to tumor cells through the antibody moiety, block the access of lymphocytes to tumor cells more effectively than antibody alone. Alternatively, the antigen portion may have a specific role in preventing lymphocyte activity on tumor cells.

In addition to blocking factor, the population of factors involved in tumor immunology includes "unblocking factor." According to the Hellströms' definition, "unblocking" simply means that one serum can abrogate the blocking activity of another. For example, serum taken from mice whose Moloney sarcomas have spontaneously regressed nullifies the blocking activity of serum from mice with growing tumors. Baldwin found similar results with serum from mice whose hepatomas had been excised and serum from mice with growing tumors. Although the evidence is not yet conclusive, unblocking factor may be free antibody. This would be consistent with Baldwin's finding that blocking does not occur in the presence of excess free antibody.

Other investigators, including Graham Currie of the Chester Beatty Institute in London and Charles McKhann of the University of Minnesota Medical School, Minneapolis, have focused on the role of tumor antigens in oncogenesis. McKhann points out that tumors may have evolved the capacity to shed large quantities of antigen as a defense mechanism against immune surveillance. McKhann and Currie think that antigens shed by tumor cells permit tumor growth by binding to receptors on lymphocytes and preventing them from attacking tumor cells. Antigen could thus inhibit immune surveillance by binding directly to lymphocytes or by forming blocking complexes with antibody, or both. The effect would be to saturate and overwhelm the immune response. This suggestion is consistent with observations that animals that have been immunized against a particular tumor can resist challenges with small doses of tumor cells but not with large ones. The immune system apparently does have a limit to its capacity to respond to antigens.

Pinning down the roles of antigen and antibody in tumor growth should facilitate rational design of immunotherapeutic approaches. Strategies to remove antigen by increasing its breakdown or to prevent its release from tumor cells might be feasible. So might strategies to increase cell-mediated or even humoral immunity. Current approaches to immunotherapy will be surveyed in the next article of this series.

One of the few investigators to challenge the current view of immune surveillance is Richmond Prehn of the Fox Chase Center for Cancer and Medical Sciences, Philadelphia, Pennsylvania. According to Prehn, weak immune responses, such as those that might occur in the initial stages of tumor growth when only a few aberrant cells are present, stimulate tumor growth rather than inhibiting it. The immune system does function as a defense against cancer, but, in Prehn's

for a New Laser Leads to an Advanced Battery

seeking a better battery, according to Adam Heller of GTE Laboratories. Rather they were evaluating the oxyhalide solvents, such as phosphorous oxychloride ($POCl_3$), as potential hosts for rare earth ions in liquid laser systems. (Rare earth ions are well known for their application in phosphors for, among other things, color television sets.) In a second generation of experiments, they attempted and succeeded in observing light emitted as a current was passed through the ion containing oxyhalide solution. In these experiments, the researchers observed that rare earth metal was being plated out onto the anode and that chlorine gas was evolved at the cathode. Recognizing they had the makings of an electrochemical cell, they tried lithium chloride and other more soluble salts, and obtained a lithium-chlorine cell which operated at room temperature in an inorganic solution. The GTE workers then began exploring other possible constituents for a lithium battery.

At this point, both the GTE researchers and the scientists at the Army Electronics Command began exploring the possibility of eliminating the use of chlorine gas as the cathode reactant by trying solid reactants, such as graphite fluoride. But the discovery that more energy was obtained from these cells than could be accounted for from the solid reactants alone led to the realization that the solvent itself was acting as a cathode reactant. Present batteries are the result of the development of a high performance carbon cathode electrode that efficiently promotes the reduction of the solvent.

Current laboratory versions of the lithium-thionyl chloride cell exhibit specific energies of the order of 500 watt-hours per kilogram, more than 50 percent higher than previous lithium–sulfur dioxide cells and more than eight times higher than the common flashlight battery. Other features include improved low temperature operation (down to $-45°C$) and voltage stability. However, Sol Gilman, one of the Army scientists working on the lithium battery, points out that problems of cell storage life and safety engineering (a lot of energy is packed into a small volume) are still to be solved to complete satisfaction.

Observers agree that the new lithium battery amounts to a significant development that could have a considerable effect in reducing the size and weight of a wide variety of electronics packages. Work is in progress at GTE and other laboratories directed toward production of commercial cells, and, although projected materials costs are low (*3*), other researchers in the battery field caution that, often, developing a manufacturable version of a battery with a low cost presents the most formidable problem of all.—ARTHUR L. ROBINSON

References

1. J. J. Auborn, K. W. French, S. I. Lieberman, V. K. Shah, A. Heller, *J. Electrochem. Soc.* **120**, 1613 (1973).
2. W. K. Behl, J. A. Christopulos, M. Ramirez, S. Gilman, *ibid.*, p. 1619.
3. N. Marincic, J. Epstein, F. Goebel, paper to be presented at the 26th Power Sources Symposium, Atlantic City, New Jersey (U.S. Army Electronics Command, Fort Monmouth, New Jersey, 1974).