Watson, but it has an additional set of ozone-destroying reactions that, unlike those involving chlorine or NO_x, can proceed at night and at lower altitudes. Moreover, bromine does not readily form the catalytically inactive species hydrogen bromide (HBr, analogous to HCl in the chlorine cycle). The result is that bromide is, molecule for molecule, a more efficient catalyst than chlorine and would be a source of considerable worry if it were to be present in the stratosphere in any appreciable quantity.

Only a few measurements of bromine compounds in the stratosphere have been made. Sedlacek, for example, finds bromine at concentrations between 7 and 12 ppt. This concentration of bromine, if it is in the form of HBr, is consistent with calculations by Michael McElroy and Steven Wofsy of Harvard University which suggest that bromine may cause a 0.5 percent reduction in the ozone concentration at present. They propose that methyl bromide (CH_3Br), widely used to fumigate agricultural land, is the source of the stratospheric bromine. Other investigators doubt that CH_3Br actually reaches the stratosphere.

The lack of any demonstrated hazard from bromine, however, does not reduce the need for a more careful scrutiny of how, and in what form, bromine and chlorine are used in human activities. Indeed, it is likely that understanding and coming to grips with the vulnerability of the earth's ozone layer to human activities has only just begun.

—ALLEN L. HAMMOND

Thymic Hormones: Inducers of T Cell Maturation

People who lack normal T cells are in a lot of trouble. This is dramatically illustrated by the case of Heather, a 5-year-old girl who suffers from thymic hypoplasia, that is, a poorly developed thymus gland. The thymus is necessary for the normal differentiation and maturation of T (for thymus-derived) cells. In May of last year, Heather's T cell count was well below normal, and she was near death from the infections that her inadequate immune system could not fight off.

Because all other therapies had failed, Heather's physicians decided to treat the girl—the first patient to be so treated—with thymosin, a hormone preparation made from bovine thymus glands. Heather's T cell count increased. Today, with continued therapy, she is leading a virtually normal life. Moreover, investigators also have evidence that thymosin deficiency may be associated with a number of diseases besides thymic hypoplasia. They include some additional immunodeficiency diseases, certain autoimmune conditions, and cancer.

Cell-mediated immunity requires T cells, also called T lymphocytes. The graft-versus-host reaction, transplant rejection, immune surveillance of tumor cells, delayed hypersensitivity to foreign antigens, and resistance to viruses all depend on this portion of the immune system. In addition, T cells aid in the regulation of humoral immunity, which is the province of B (for bone marrow) cells, the second class of lymphocytes.

When properly stimulated by antigens, B cells differentiate into antibody-secreting cells called plasma cells. Antibodies act on a number of antigens, including bacteria and viruses. Helper T cells are needed for synthesis of many antibodies, whereas another functional class of T cells, the suppressor T cells, may repress antibody production.

Some T cells mature within the thymus itself, but there is evidence that others need not enter this gland in order to differentiate. One way that the thymus effects the maturation of T cells is through the secretion of a hormone or—more likely—hormones. About 10 years ago, when they were both working at Albert Einstein Medical College, Allan Goldstein, now at the University of Texas Medical Branch in Galveston, and Abraham White, currently at Stanford University School of Medicine, discovered thymosin. Goldstein now supplies the thymosin preparations to Heather's physicians, Arthur Ammann and Diane Wara of the University of California Medical School in San Francisco, and also to most other investigators studying the action of the hormone. The material that has been used for these investigations is a partially purified preparation designated thymosin fraction 5 but often simply called thymosin.

Found in Several Species

Although Goldstein and his colleagues have identified thymosin in a number of species, including the mouse, rat, rabbit, and human, they usually extract the hormone from bovine thymus. Thymosin activity does not appear to be species-specific. The Galveston group has recently purified a single active component (thymosin fraction 8) from fraction 5. It is a polypeptide containing about 108 amino acids and weighing 12,200 daltons. Residues of glutamic and aspartic acids, the acidic amino acids, constitute about 50 percent of the molecule.

There are indications that fraction 5 may contain more than one active component. It contains at least 11 other acidic polypeptides, weighing from 1,200 to 14,000 daltons, in addition to the one purified. Goldstein said that this latter material may be less active in some assays than the less pure fraction 5. This could mean that active components have been lost during purification or that the procedures have altered the material with consequent loss of activity.

Administration of thymosin fractions can substitute, at least partially, for a functional thymus gland. Ammann said that weekly injections of thymosin fraction 5 have maintained Heather's T cell count at a near-normal level and have corrected some of her deficient immune reactions; others remain unchanged, however.

Bovine thymosin preparations also alleviate immunodeficiencies in mice. Thymectomized newborn mice usually die from infections and a wasting disease. Goldstein and his colleagues found that partially purified thymosin preparations reduce the incidence of wasting disease and death in such animals and partially restores their cell-mediated immunity. Thymosin administration to newborn mice accelerates the development of their T cell functions. The animals can resist the growth of virus-induced tumors, and their spleen cells, when injected into mice of another genetic type, can mediate a graft-versus-host reaction at an earlier age than normal. (The spleen stores T lymphocytes.)

Thymosin, or at least thymosin-like activity, can be demonstrated in the blood of animals and humans, according to Jean-François Bach and his colleagues at the Hôpital Necker in Paris. This activity disappears rapidly from the circulation of mice following thymectomy.

In the human, the size of the thymus reaches a peak before puberty and then decreases with increasing age. Cell-mediated immunity also decreases with age. Many investigators think that these events are causally related to the increased incidence of infections, autoimmune disease, and cancer that accompanies aging. Bach has shown that thymosin activity decreases as normal mice age. Goldstein, in collaboration with Bach, showed that the concentration of circulating hormone declined with age in man and other mammals.

An in vitro technique can be used to estimate what proportion of blood lymphocytes are differentiated T cells. It involves mixing isolated lymphocytes with sheep red blood cells. The red blood cells bind to mature T cells to form rosettes (called T or E rosettes) that can be counted.

Predicting Responses to Thymosin

Wara and Ammann found that the technique may be used to predict whether thymosin can improve the T cell status of a patient with a deficiency of these cells. If the patient has immature T cells that will differentiate in response to the hormone, addition of thymosin to the assay system will increase the number of T rosettes. This is what happened with Heather's lymphocytes in vitro, and therapy with thymosin did significantly improve her condition.

Lymphocytes from patients with a number of other immunodeficiency diseases, including DiGeorge syndrome, ataxia telangiectasia, and Wiskott-Aldrich syndrome, also respond in the in vitro assay. But not all do. Lymphocytes from patients with severe combined immunodeficiency disease, in which both cellular and humoral immunity is lacking, do not produce increased numbers of T rosettes in the presence of thymosin. Presumably the defect in lymphocyte differentiation that causes this condition occurs prior to the development of the T cell precursor that responds to thymosin.

Evan Hersh, Larry Schafer, and Jordan Gutterman of the University of Texas M. D. Anderson Hospital and Tumor Institute have used a different assay, one that measures cell-mediated immunity, to investigate the effects of thymosin on lymphocytes. If the activity of lymphocytes, whether they are taken from normal individuals or cancer patients, was low when determined by this assay, addition of thymosin to the system boosted the responses. In contrast, thymosin actually suppressed the responses of lymphocytes that were vigorously active without added hormone.

The mechanism of thymosin action is not completely understood, but it appears that the hormone converts immature T cells into mature forms that are immunologically active. Because thymosin works very quickly, Goldstein thinks that it derepresses or activates cells that have already been programmed to differentiate into T cells.

Several investigators suspect that thymosin works through adenylate cyclase and adenosine 3′,5′-monophosphate (cyclic AMP). Bach, Goldstein, and others have found that cyclic AMP can mimic some of the functions of thymosin. Hersh said that experiments performed by Nathan Trainin at the Weizmann Institute in Israel indicate that a feedback mechanism could be operating. Thymosin may stimulate the enzyme adenylate cyclase to make cyclic AMP and increase the number of functional T cells. If the cyclic AMP concentration goes too high, thymocyte function could be inhibited. This may be why thymosin sometimes inhibits the responses of lymphocytes.

Thymosin Deficiency and Cancer

Cancer patients are known to suffer from a variety of immunodeficiencies, especially of cellular immunity. For some of them, these deficiencies may be the result of insufficient thymosin. Paul Chretien of the National Cancer Institute used the T rosette assay to survey the T cell status of 200 patients with different types of localized cancers. Patients with carcinomas of the head and neck, lung, uterine cervix, and esophagus had lower than normal percentages of T rosettes; addition of thymosin to the assay systems produced a rapid increase in the number of rosettes. Lymphocytes from patients with melanoma, prostate, or bladder cancer did not respond to thymosin, however. Chretien thinks that the assay can be used to identify cancer patients for whom thymosin therapy may be beneficial. The idea is that thymosin would stimulate their cellular immunity and help prevent the spread of the cancer or aid in producing a better response to other cancer therapies.

There is as yet no evidence that thymosin will actually benefit cancer patients. Only 26 persons are currently receiving the hormone. They include 15 patients with advanced metastatic cancer who have been treated by the group at M. D. Anderson Hospital. Goldstein said, however, that plans for a much more extensive, coordinated study are being made.

Hoffmann-LaRoche in Nutley, New Jersey, will produce enough thymosin to treat 250 patients suffering from cancer, or immunodeficiency or autoimmune diseases, during the first year of the study. The primary goals of the study, which is classed as a phase I clinical trial as specified by the Food and Drug Administration, are to determine the safety of thymosin therapy and to learn what immunological effects, if any, it produces. Determining safety and effective doses are the goals of all phase I clinical trials.

Adjuvant to Cancer Therapies?

Another potential use of thymosin is bolstering the cellular immunity of cancer patients undergoing chemotherapy or radiation therapy. Both types of regimens are immunosuppressive and depress T cell activity at just the time that patients may need it to eliminate residual tumor cells and prevent metastases. A number of investigators, including Hersh, have evidence that, in general, a good prognosis correlates with a high level of cellular immunity. Chretien has found that addition of thymosin to lymphocytes from patients whose cellular immunity has been depressed by radiation can induce an increase in the number of T rosettes in the in vitro assay. He thinks that trials to determine whether thymosin administration to patients undergoing radiation therapy can prevent or ameliorate the decline in T cells are warranted.

Evidence that defective T cell function is involved in the etiologies of autoimmune diseases is also accumulating. Autoimmunity results when the immune system loses its tolerance for self and attacks the body's own tissues. Autoantibodies (antibodies against self) are present. Many investigators are coming to the conclusion that suppressor T cells normally prevent the production of autoantibodies and that a deficiency of these T cells contributes to the development of autoimmunity. (Suppressor T cells will be discussed

more fully in a future article.) Included among the conditions thought to be of autoimmune origin are rheumatoid arthritis, systemic lupus erythematosus (SLE), certain anemias, late-developing diabetes, and multiple sclerosis.

Systemic lupus erythematosus afflicts an estimated 400,000 to 500,000 people; about 80 percent of whom are women, and usually develops between the ages of 20 and 40. It can be mild but in its severe form the disease is both debilitating and life-threatening.

Investigators studying SLE frequently use the New Zealand Black (NZB) mouse. Between the ages of 5 and 9 months, mice of this strain spontaneously develop an autoimmune disease that closely resembles human SLE. The animals have LE cells (a type of white blood cell characteristic of SLE), antibodies to nucleic acids, hemolytic anemia, and immune complex glomerulonephritis, an inflammation of the kidney caused by deposition of antibody-antigen complexes. About 10 percent of NZB mice also develop a malignant lymphoma analogous to chronic lymphocytic leukemia.

According to Norman Talal, Michael Dauphinee, and their colleagues at the University of California Medical Center, NZB mice progressively lose T cell functions. Even before autoimmunity is clinically detectable, their T cells are developmentally and functionally abnormal. Bach found that thymosin-like activity in serum declines at an abnormally early age in NZB mice; it is negligible by the time they are 2 months old. This implies that the thymosin deficiency causes abnormal T cell development and, consequently, autoimmunity.

Humans with active SLE may also be deficient in thymosin. Edgar Cathcart and Morton Scheinberg of Boston University Hospital showed that lymphocytes from patients with active SLE formed fewer T rosettes in vitro than did those from healthy controls or from patients with rheumatoid arthritis or inactive SLE. The SLE patients had more of what the investigators call "null" cells, that is, cells with neither B nor T marker antigens. Treating the lymphocytes in vitro with thymosin fraction 5 increased the number of T rosettes formed and decreased the number of null cells.

Talal hypothesized that administration of thymosin fraction 5 to NZB mice might correct their T cell deficiencies and prevent the onset of autoimmunity. It did restore to normal one of the aberrant developmental responses of NZB thymocytes; however, thymosin delayed, but did not prevent, the development of autoimmune disease in the animals. Talal said that additional factors probably play a role in the etiology of autoimmunity in NZB mice. These could include genetic disposition and viruses, both of which have been implicated in the etiologies of several autoimmune conditions. Other investigators have shown that NZB thymocytes are infected with murine leukemia virus. Viral infection could destroy the cells or cause them to function abnormally.

Another possibility is that a hormone or hormones not present in fraction 5 may be involved. This preparation did not correct all of Heather's immunodeficiencies either. Other investigators have isolated thymic hormones that are involved in T cell differentiation. For example, Gideon Goldstein,

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Ceramics: Brittle Materials for High Temperature Structures

Two of the world's most pressing problems—the increasing cost and decreasing availability of fossil fuels and the pollution of the environment resulting from their use—could be partially solved if the operating temperature of a heat engine were raised. More useful work for the same amount of fuel consumed would be obtained because of the engine's increased thermal efficiency, and fewer pollution-causing emissions would be released because of the more complete combustion permitted by richer fuel to air ratios.

Unfortunately, even the most exotic high temperature alloys (super alloys containing large amounts of nickel, cobalt, or chromium) cannot withstand temperatures in excess of about 1100°C. However, as a result of advances made over the past 15 years, refractory ceramic materials based on silicon nitride (Si_3N_4) and silicon carbide (SiC) are being considered for use as high temperature structural materials in places where previously only metals would have been used. Most current research is oriented toward ceramic gas turbines for vehicles, stationary power generators, and remotely piloted aircraft.

As compared with metals, ceramics are more resistant to high temperatures, oxidation, corrosion, and erosion, and are quite strong, but they are quite brittle. In particular, when rapid temperature changes occur, ceramics tend to fracture under the resulting thermal stresses, a condition known as thermal shock. Moreover, the virtual absence of plastic deformation that can relieve stress concentrations in brittle materials means that the stresses must be accurately known everywhere in a part, so that design is a formidable problem. As a result, interest in ceramics as structural materials has been a cyclical phenomenon since about 1900.

Interest in silicon carbide and silicon nitride derives from their having a combination of moderate-to-low linear thermal expansion coefficients and high-to-moderate thermal conductivities respectively. These ceramics are thus less susceptible to thermal shock than other such materials. But because both compounds decompose by sublimation at high temperatures, parts cannot be fabricated by casting, thus necessitating recourse to powder metallurgical methods, such as sintering or hot-pressing.

In the mid-1950's, workers at the Admiralty Materials Laboratory in the United Kingdom discovered that relatively dense silicon nitride with good properties could be made by reacting silicon powder in a nitrogen atmosphere at high temperature. The first step in this so-called reaction bonding or reaction sintering process is the compacting of the silicon powder into the desired shape. An organic binder or plasticizing agent (which is later burned off) is mixed with the silicon powder to hold it together and to permit the formation of complex shapes through use of processes such as injection molding, which is common in the plastic industry. This "green" body is heated first to 1350°C and then to 1450°C to bring about the nitridation reaction.

Silicon nitride parts made in this way are about 70 to 85 percent of the maximum possible density and maintain their mechanical strength up to about

fairs, University of Illinois College of Medicine, to dean, Mercer University School of Medicine. . . . **C. Mel Adams**, professor of materials engineering, University of Wisconsin, Milwaukee, to dean, College of Engineering, University of Cincinnati. . . . **Donald F. Tapley**, professor of medicine, Columbia University, to dean, Columbia University Faculty of Medicine. . . . **Hla Shwe**, chairman, physics department, East Stroudsburg State College, to dean of science at the college. . . . **Roy B. Levow**, assistant professor of mathematics, Florida Atlantic University, to chairman, mathematics department at the university. . . . **Robert N. Berk**, associate professor of radiology, University of California, San Diego, to chairman, radiology department, University of Texas Health Science Center. . . . **Louis Kriesberg**, professor of sociology, Syracuse University, to chairman, sociology department at the university. . . . **Douglas E. Kelly**, chairman, biological structure department, University of Miami School of Medicine, to chairman, anatomy department, University of Southern California School of Medicine.

RECENT DEATHS

Norma J. Adamo, 47; associate professor of anatomy, Louisiana State University; 25 October.

Charles Aikin, 73; former chairman, political science department, University of California, Berkeley; 24 November.

Carl B. Allendorfer, 63; professor of mathematics, University of Washington; 29 September.

Rupert S. Anderson, 76; former research physiologist, U.S. Army Biomedical Laboratory, Edgewood Arsenal; 16 October.

Wilfred H. Baker, 62; former professor of civil engineering, West Virginia University; 5 November.

Ralph Colp, 81; former clinical professor of surgery, College of Physicians and Surgeons, Columbia University; 11 November.

LeRoy L. Constantin, 39; professor of physiology and biophysics, Washington University School of Medicine; 7 November.

George S. Counts, 84; professor emeritus of education, Columbia University; 10 November.

Rex Cox, 86; former professor of agricultural economics, University of Minnesota; 29 October.

Hunter Guthrie, 73; former president, Georgetown University; 11 November.

Jarvis B. Hadley, 65; research geologist, U.S. Geological Survey; 14 November.

Conrad Hammar, 79; former professor of agricultural economics, University of Minnesota; 5 November.

Roger G. Hart, 46; biophysicist, bio-medical division, Lawrence Livermore Laboratory; 10 November.

L. Emmett Holt, Jr., 79; former chairman, pediatrics department, New York University School of Medicine; 30 November.

Myron R. Karon, 42; professor of pediatrics, University of Southern California School of Medicine; 16 November.

M. Gertrude Keckeissen, 65; professor of psychology, College of Mount St. Vincent; 17 November.

Robert C. Kinter, 74; professor emeritus of chemical engineering, Illinois Institute of Technology; 15 October.

Erich Lindemann, 74; visiting professor of psychiatry, Stanford University School of Medicine; 16 November.

Gerald MacCarthy, 77; former professor of geology, University of North Carolina, Chapel Hill; 31 October.

Ray S. Marsh, 79; professor emeritus of horticulture, West Virginia University; 2 November.

Robert E. McKechnie, 68; former chancellor, University of British Columbia; 17 October.

Imogene E. Okes, 52; education specialist, U.S. Office of Education; 22 October.

James R. Patrick, 81; professor emeritus of psychology, Ohio University; 3 August.

William B. Snow, 79; retired professor of physical medicine, Columbia University; 16 November.

Charles K. Trueblood, 81; former chairman, psychology department, American University; 1 November.

Jerome P. Webster, 86; professor emeritus of clinical surgery, College of Physicians and Surgeons, Columbia University; 14 November.

Howard B. White, 62; former dean, graduate faculty of political and social sciences, New School for Social Research; 4 November.

Irvin G. Wyllie, 54; chancellor, University of Wisconsin–Parkside; 25 October.

Frederick F. Yonkman, 72; former chairman, pharmacology department, Wayne State University; 16 September.

RESEARCH NEWS

(Continued from page 1185)

now at Sloan-Kettering Memorial Institute, has purified two polypeptides, thymopoietin I and II (formerly called thymin I and II) from bovine thymus gland. The two polypeptides have very similar chemical and biological properties.

The precursors of T cells are formed in bone marrow. Gideon Goldstein and Ross Basch of New York University School of Medicine found that bone marrow cells rapidly acquire surface antigens characteristic of mature T cells when they are incubated with very low concentrations of thymopoietin I or II. As little as 2 nanograms of polypeptide per milliliter of culture medium produces a maximal response. With David Schlesinger of Massachusetts General Hospital, Gideon Goldstein has now determined the amino acid sequence of thymopoietin II, which weighs 5550 daltons, and has synthesized a biologically active molecule.

Nonspecific Thymic Polypeptide

Gideon Goldstein, Edward Boyse, and their colleagues at Sloan-Kettering have isolated yet another thymic polypeptide that induces T cell differentiation. This one, however, also induces B cell maturation and is found in every cell type, including plant cells and bacteria, that they have examined. The investigators have named the material ubiquitous immunopoietic polypeptide (UBIP). Because of its lack of specificity and its presence in organisms that have no immune systems, they do not think that UBIP functions physiologically in the differentiation of T cells. The capacity of this substance to stimulate T cell differentiation points up the caution that must be exercised in identifying physiological inducers of differentiation.

Nevertheless, there is strong evidence that an endocrine deficiency—a lack of thymosin or other thymic hormones —contributes at least partially to the etiologies of immunodeficiency and autoimmune diseases, cancer, and even the degenerative changes of old age. All this raises the as yet unproven but still exciting possibility that hormonal replacement therapy can help control these diseases just as insulin controls diabetes. It also means that the thymus gland, once thought to be about as useful as the human appendix, may well be the master gland of the immune system.—JEAN L. MARX