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Scientist In The Making: [Dr. Alice Bendix Gottlieb]

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THE ROCKEFELLER UNIVERSITY

RESEARCH

PROFILES

FALL 1981

"A continuing tide of young people moving into research is crucial to the vitality of science... Their enthusiastic curiosity is the oxygen required to keep the flame bright."

DR. DONALD S. FREDERICKSON
Former Director
National Institutes of Health

Scientist In The Making

Twenty-nine-year-old Alice Bendix Gottlieb, a "beeper" tucked in the pocket of her white coat and a stethoscope around her neck, looks much like other second-year medical residents. Unlike most, however, her professional equipment also includes a doctorate in immunology. In 1979, when she stood up to receive her Ph.D. at The Rockefeller University, her name was already attached to nine published papers. A year later, Cornell University Medical College awarded her an M.D. and the Sarah O'Laughlin Foley Prize in Clinical Medicine. When she completes her residency next spring, she will resume research at The Rockefeller University as part of a two-year fellowship in rheumatology at the Hospital for Special Surgery.

Dr. Gottlieb is a clinical scientist in the making, a physician-researcher shuttling between the hospital ward and the laboratory. She is a graduate of the joint Rockefeller-Cornell M.D.-Ph.D. program, an extension of a commitment to clinical research that began in 1910 when the then Rockefeller Institute for Medical Research opened the country's first hospital devoted to the study of the basic science of human disease.

As a child, reading biographies of famous medical researchers of the past, many of whom were involved in developing vaccines for immunization, Alice Bendix was enthralled by the idea that the body can produce antibodies to



protect itself against infectious organisms. Later she would learn how radically contemporary immunology has changed that simple picture. For one thing, researchers have discovered that the immune defense system can itself become the agent of disease through the process called autoimmunity—rejection of “self.” Among the conditions known or suspected to be of autoimmune pathogenesis are rheumatoid arthritis, myasthenia gravis, juvenile-onset diabetes, some forms of hepatitis, and systemic lupus erythematosus. This last has been under investigation at The Rockefeller University for a number of years as the prototype of the autoimmune process, and was the major part of Alice Gottlieb’s doctoral research.

THE BITE OF THE WOLF

Lupus is the Latin word for wolf. Erythematosus refers to reddening of the skin caused by capillary congestion. Systemic lupus erythematosus (SLE) was so named because of the customary red rash on the face of its sufferers, which to diagnosticians in the 19th century resembled the bite of a wolf. An inflammatory disease, SLE can affect almost any organ in the body—blood, brain, muscles, joints, kidneys, lungs, heart, and skin. A mild form of lupus, called discoid, affects only the skin. In its most serious form, SLE can be fatal. An estimated half-million Americans have it. There are treatments of varying degrees of effectiveness, but no preventive technique or cure.

In normal immune function, an elaborate defense arsenal rushes into action when outside antigens attack the body. Any molecule the body perceives as foreign or “non-self” is called an antigen. White blood cells, including lymphocytes, are the principal defenders. B cells are lymphocytes that are believed to be formed in the bone marrow. When activated they differentiate into plasma cells that produce antibodies, which, circulating through the blood, bind to antigens. (Vaccines are derived from antigens. Vaccinations stimulate the body to make antibodies which will then protect the body if it is exposed to an attack by the microorganisms, such as bacteria

or viruses, that transmit those particular antigens in nature.) T cells are also probably formed in the bone marrow but then travel to the thymus, where they are processed to perform other jobs. T cells are responsible for what is called cell-mediated immunity, the rejection of foreign tissues, including transplants. Another group of white cells, among them macrophages and dendritic cells, are also part of the cell-mediated system. The functions of the T and B lymphocytes, although distinct, overlap. T cells modify the action of B cells by facilitating or suppressing antibody production. The macrophages are stimulated by antibodies to engulf invaders. A group of enzymes in the blood, collectively called complement, are also activated by the antibodies and deliver the chemical coup de grace to the antigens. When antibodies are no longer needed, a signal goes out to stop production.

In the process of autoimmunity, antibodies pour forth and attack the body’s own molecules, binding to them as they would to true antigens. As antibody and antigen bind together, they form what is called an immune complex. By studying patients with SLE, great advances have been made in understanding how immune complexes cause tissue injury. These patients produce a wide range of autoantibodies, including those directed against their own DNA, RNA, ribosomes, red cells, and white cells. (DNA—deoxyribonucleic acid—is the genetic material of the cell. RNA is a class of nucleic acid with various functions, including conveying the DNA message to the ribosomes, the cell components involved in protein production.) Antibodies to DNA have proven to be of special interest. Studies in Dr. Kunkel’s laboratory demonstrated that anti-DNA antibodies, in the form of immune complexes, were concentrated in the glomeruli (filtering apparatus) of kidneys from patients with SLE nephritis—clearly demonstrating the role of autoantibodies and immune complexes in the pathogenesis of this disease. This discovery has been extended to other autoimmune diseases such as rheumatoid arthritis.

“We know,” Dr. Gottlieb points out, “that in normal individuals there can be low levels of autoantibodies, but in patients with SLE, these levels are much higher and they actu-

ally cause significant tissue injury." Current research efforts are focused on the abnormality of the immune regulatory system that causes SLE patients to make such an abundance of antibodies to their self-constituents.

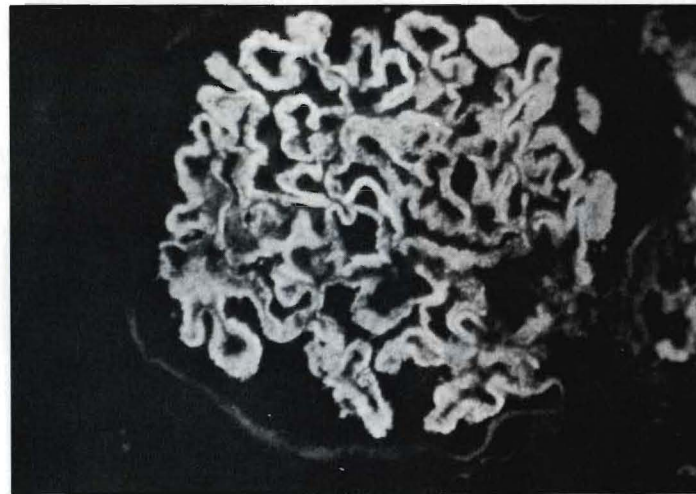
"Studies of human disease are most difficult," says Dr. Gottlieb, "and it is essential to acquire the best possible training." Hers began early, at New York's highly acclaimed Bronx High School of Science. She earned her bachelor's degree at Brandeis University from which she was graduated summa cum laude (and where she met and married mathematician Allan Gottlieb). At college, she majored in chemistry, learning laboratory skills but acquiring little clinical experience. In her first year as a graduate fellow at Rockefeller University, she worked with Professor Richard M. Krause, who has since become director of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, to master the basic techniques of immunology. With Dr. Thomas J. Kindt, now also at NIH, she developed an improved radioimmune assay for the study of antibody diversity in experimental animals. Then she joined the laboratory of Professor Henry G. Kunkel to apply her knowledge to the study of human disease. Dr. Kunkel, Abby Rockefeller Mauze Professor and a senior physician of The Rockefeller University Hospital, has, in the words of one of his colleagues, "contributed more to the understanding of immunologically mediated human diseases and basic principles of human immunology than any other investigator in the field." He is also a teacher with an exceptional capacity for recognizing and nurturing scientific talent.

TRACKING THE T CELLS

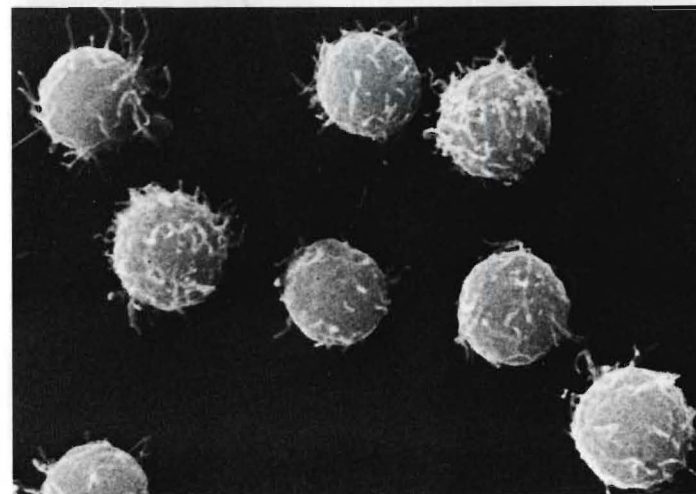
One of the studies Alice Gottlieb participated in during the course of her training with Dr. Kunkel resulted in demonstrating that SLE patients have impaired ability to respond to outside antigens as the result of a defect in T-cell function. This was learned by applying an *in vitro* (test tube) assay for measuring the cellular immune response of the blood cells to

the antigen tetanus toxoid, a method that's been used in Dr. Kunkel's laboratory to study a number of problems.

"When samples of blood from normal people are exposed to tetanus toxoid" explains Dr. Gottlieb, "there is a marked proliferation of T cells. This proliferation also involves the presence of an accessory cell, the exact nature of which is still



Glomerulus from the kidney of a patient with SLE nephritis that has been treated with a fluorescent anti-immunoglobulin antiserum. The white areas show the deposition of autoantibodies.



Lymphocytes.

unknown. Some interesting research is going on in Zanvil Cohn's laboratory to find out what this accessory cell is. (Professor Zanvil A. Cohn is the leader of the University's laboratory of cellular physiology and immunology). In contrast, the T cells from SLE patients showed a significant inability to proliferate in response to antigenic stimulation. SLE patients whose disease was inactive also showed the defect."

Was the defect in the T cells themselves or in the accessory cells? With the help of Dr. Robert Lahita, a fellow laboratory member, Dr. Gottlieb located families of "histocompatible" siblings, one normal and one with SLE, to try to answer this question. The world histocompatible refers to a biological phenomenon of growing interest and importance in immunological research. In cell-mediated immunity, the immune system recognizes certain antigens on the surface of foreign cells as non-self, in the same way it recognizes the foreign nature of bacteria or viruses. The antigen molecules thus recognized are called histocompatibility antigens, and they differ from individual to individual. They are what gives the tissues of each person his or her chemical identity, or biological uniqueness. Except for identical twins, close or exact histocompatible matches are rare.

"We found" says Dr. Gottlieb, "that SLE accessory cells were perfectly able to cooperate with the histocompatible normal T cells and give a good proliferating response to antigen. But SLE T cells added to the normal accessory cells could not. It was clear that the reason why the cell-mediated immune function was defective was because the T cell was defective. Further studies showed that the T-cell defect was largely independent of adsorbed anti-lymphocyte antibody or immune-complex inhibition or prostaglandin suppression of T-cell function."

Another aspect of her thesis work included studying the role of isolated B-cell subpopulations from normal individuals in various *in vitro* immune systems and comparing them with the cells from patients with chronic lymphocytic leukemia (CLL), a malignancy characterized by the overproduction of surface immunoglobulin (sIg)-bearing B cells. (Immunoglobulins are antibodies.) In association with Drs. James

Halper and Shu Man Fu, Dr. Gottlieb demonstrated marked differences in the membrane properties of sIg-bearing B lymphocytes from the two sources. Qualitative differences of this kind between malignant and normal cells may offer new leads to our understanding of cancer.

AN IMPORTANT DECISION

The study of immune complex disorders fascinates scientists like Dr. Gottlieb because there are so many facets to explore. In SLE, for example, the incidence of disease is nine times greater in women of child-bearing age than in men. In studies with Professor Jack Fishman, head of Rockefeller University's endocrinology laboratory, it was observed that there is also a high incidence of SLE among men with Klinefelter's disease, a condition in which there is an extra female component on the chromosome. More recently Dr. Lahita, in continued collaboration with Dr. Fishman's laboratory, has shown that SLE patients have a higher than normal level of metabolized estrogen, the female hormone. All of this strongly suggests that estrogen plays a role in the manifestation of SLE, an area of investigation that is being vigorously pursued. Then there remains the provocative matter of histocompatibility. Other research is underway to understand how the presence of certain histocompatibility types relates to a heightened immune-system response to a given antigen, which occurs in normal individuals, as well as those with autoimmune diseases.

There will be plenty for Alice Gottlieb to do when she returns to the laboratory. In the meantime, she runs to hospital rounds, takes care of patients, and responds to calls on her beeper. As she says: "Joining the M.D.-Ph.D. program and having the opportunity to work at Rockefeller University was one of the most important decisions I've ever made. The deepest understanding is achieved when basic research is applied to the study of disease states and, conversely, the basic scientist with a knowledge of clinical medicine enjoys the privilege of using these 'experiments of nature' to understand normal human biology."

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