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Commentary on *the Langerhans Cell in Contact Hypersensitivity*

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The origin and function of Langerhans cells remained elusive for many years after their discovery by Paul Langerhans in 1868. It was not until 1961 that an ultrastructural marker of Langerhans cells in the form of a unique organelle was described [1]. Subsequently, while conducting an electron-microscope study of contact allergic reactions in humans [2], Dr. Inga Silberberg-Sinakin and her colleagues noted apposition of lymphocytes to Langerhans cells, suggesting a role for Langerhans cells in immunologic reactions. This paper summarizes an interview with Drs. Inga Silberberg-Sinakin and Rudolf Baer early in 1988, discussing their reminiscences concerning this seminal observation and its implications for Langerhans cell research.

During her early studies of the topical application of mercuric chloride in humans, Dr. Silberberg-Sinakin observed that there was apposition of lymphocyte-like cells to Langerhans cells in the epidermis of individuals with contact allergic reactions but not of those individuals with irritant reactions or of normal subjects [2]. She remembers that it was a troublesome finding to evaluate because findings observed on electron microscopy are difficult to statistically quantitate. Therefore, she proceeded to study a variety of contact allergens in humans [3] and to seek and exploit an animal model [4]. In studies of guinea pigs sensitized to dinitrochlorobenzene (DNCB), subsequent passive transfer experiments with a time-course analysis demonstrated Langerhans cells in dermal lymphatics [5,6], a finding that strengthened the interpretation of an immunologic role for the Langerhans cell.

At that time, very little was known about the biologic functions of the Langerhans cell. As background, Dr. Baer recalled that as early as 1875, Ranvier speculated that Langerhans cells were derived from lymphocytes. However, subsequent informed opinion was that Langerhans cells were effete melanocytes. Then it was recognized that Langerhans cells could be identified by electron microscopy based on the key feature of a distinctive cytoplasmic organelle [1], that the cell membrane of Langerhans cells contained ATPase [7]; and that Langerhans cell granules were endocytotic organelles [8].

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Dr. Silberberg-Sinakin went on to say that the initial recognition of the morphologic observations led her and her collaborators at New York University School of Medicine (Dr. Jeanette Thorbecke and Dr. Baer) to suggest that the Langerhans cell was the potential antigen-presenting cell in the skin that people had been seeking. Dr. Silberberg-Sinakin added her perspective on the controversies involved in the acceptance of this work. She stated that there was support within the Department of Dermatology at New York University School of Medicine and among immunologists and cell biologists. Within the general dermatologic community, however, there was reluctance to accept this new immunologic function of the Langerhans cell.

Both Dr. Silberberg-Sinakin and Dr. Baer went on to state that the studies which involved the uptake of ferratin by Langerhans cells and their migration through dermal lymph vessels to the lymph node were not only of great importance in elucidating the fate of antigens taken up in the epidermis and how they migrate to the regional lymph nodes [9,10], but also was the first work that showed a applicability to contact allergy [11]. Although contact allergy has been a model for studying the fate of many different kinds of antigens, it also suggested that in delayed-type hypersensitivity, reactions in general Langerhans cells could serve the same functions. Presumably, larger molecules, such as tumor antigens and microbial antigens such as viruses and fungal antigens, are taken up by Langerhans cells [12]. This function also applies to transplantation antigens, and it has been shown that Langerhans cells play a role in graft rejection [13] in the skin. Moreover, Langerhans cells could be target cells [14], and the damaging effects could be caused by lymphocytes or immune complexes plus complement [14]. In addition, certain physical agents and substances are capable of depressing the functional capacity of Langerhans cells [I5–19]; notably ultraviolet A and ultraviolet B and the topical or systemic administration of glucocorticosteroids [20]. There are also different numbers of Langerhans cells in various skin sites. Areas with diminished numbers of Langerhans cells are not able to mount contact reactions [21].

After the observation that Langerhans cells were antigen-bearing cells, Dr. Silberberg-Sinakin said that she and her colleagues reviewed the literature on antigen-bearing or antigen-presenting cells (such as indeterminant dendritic cells, interdigitating reticular cells, follicular dendritic reticular cells described by Nossal, and dendritic cells described by Steinman and Cohn) in other organs such as lymph node,

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spleen, and thymus and postulated that some of these cells could be relatives of each other and that knowledge of one cell type may be applicable to others [22]. Dr. Baer concurred that there have been developments in the role of dendritic cells in other organs so that today one can talk about a dendritic cell system. The dendritic cells in lymph nodes, thymus, spleen, Kupffer's cells in the liver, and veil cells in the intestines, are all parts of a large system of dendritic cells [22]. The question has arisen as to whether some of these cells are derived from Langerhans cells. It has been shown [23] that cultured Langerhans cells go through certain maturational transformations and that they resemble lymphoid dendritic cells, suggesting that the maturation of stimulatory function within the dendritic cell lineage represents an important control point in the induction phase of cell-mediated immunity. Apparently, all of these dendritic cells have the capacity to present antigens, and they are much better at this than cells of the macrophage-monocytes series, he added. Depending on the site in which these dendritic cells are located, there are certain differences; however, they are at poor phagocytes and good at pinocytosis and endocytosis. What is termed processing antigens is actually the endocytosis of these particles [24,25] followed by processing them chemically and returning them to the surface. The Langerhans cell is the foremost type of dendritic cell involved in this function, he said.

Dr. Baer went on to say that, regarding clinical application, there is now an increasing interest in aging, and that the demonstration of the waning immunologic capacity of human beings as they get older, at least in part, may be due to fewer Langerhans cells. There seems to be a decrease in Langerhans cells in older humans [26]. Moreover, there is evidence that there is a difference in the number of functioning Langerhans cells between young and old mice [27].

Dr. Baer said that there were some very basic things that are still in a primitive state of knowledge. For example, it is not known whether Langerhans cells are one particular cell line or whether there are different varieties with, perhaps, different functions. An important development arising from the Langerhans cell studies is that another dendritic cell has been discovered known as the Thy 1^+ cell. Although this cell only has been found in mice to date [28–30], there is most certainly an equivalent in human beings and in other species. These Thy 1^+ cells are important because they may be the antigen-presenting cells for suppressor cells, in contrast to the Ia^+ Langerhans cells [31–33], which are the antigen-presenting cells for CD_4^+ T cells and for delayed-type hypersensitivity.

Dr. Baer went on to say that after it became evident that CD_4^+ T cells were destroyed by the human immunodeficiency virus (HIV), it was shown that the number of epidermal Langerhans cells in cutaneous biopsy specimens from patients with acquired immunodeficiency syndrome (AIDS), AIDS-related complex (ARC), and high-risk patients who had no evidence of AIDS or ARC [34], as assessed by examination of Ia antigens and membrane ATPase, was diminished. A possible reason for the observation that Langerhans cells are effected in AIDS may be that Langerhans cells also have the CD4 (T4) receptor [35,36]. The HIV virus enters the T cells by attaching to the CD4 receptor [37,38], suggesting that the virus also can enter the Langerhans cells via this receptor. He concluded that a major impact of the research on the Langerhans cell has been on the general knowledge about the skin. This includes the recognition that the skin is a major immunologic organ and the fact that the Langerhans cell is one of the features that seems to make it so.

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