Six Citation Classics from The Journal of Investigative Dermatology

The absolute number of citations is only one indicator of the importance of a particular paper, and is often not the most important measure of how a particular paper influences subsequent scientific development or the application of basic and applied science to clinical practice. The Editors have selected six highly cited papers from the 200 most cited articles in the JID as “Citation Classics.” These are papers of high impact which demonstrate in different ways how simple observations can generate wide and expanding effects. They represent a varied selection of papers, including basic research in cell biology and immunodermatology, a clinical trial, development of new techniques in cell biology and pharmacology (“methods” papers), and a review article. Accompanying the first page of each of these Citation Classics is an invited commentary on the importance of the paper to cutaneous biology. Each of these six Citation Classics represents an important advance in cutaneous biology.

The first Citation Classic is the most cited paper in the JID, entitled “The Identification of Contact Allergens by Human Assay. III. The Maximization Test: a Procedure for Screening and Rating Contact Sensitizers” [1] by Albert Montgomery Kligman. The development of the maximization test is an excellent example of the application of extensive knowledge of contact hypersensitivity to the development of a practical assay of drugs as contact sensitizers. The applicability of this assay was based on its foundation in science, its extensive testing, and its eventual reliability. The high profile of this paper also illustrates the strong relationship between cutaneous biology, investigative dermatology, and the pharmaceutical and cosmetics industries. A highly predictive and reliable assay such as the maximization test is essential to the pharmaceutical and cosmetics industries. In the twenty years since this paper was published, the partnership between cutaneous biologists and industry has grown considerably. In 1988 some of the best science relating to cutaneous pharmacology was performed in industrial laboratories, and was often published in the JID.

The second paper selected for commentary is “Oral Methoxsalen Photopheresis for the Treatment of Psoriasis: A Cooperative Clinical Trial” [2] by John W. Melski and 32 other participating investigators. This paper is the third most cited paper in the JID, and is a follow-up to a paper published in the New England Journal of Medicine [3], which is one of the most highly cited papers in the history of that journal. No recent new treatment in dermatology has had greater impact than PUVA, and this impact is thoroughly documented in the commentary by Jeffrey Bernhard. The “PUVA Story” is a clear demonstration of how basic research can lead to new clinical treatments, how better understanding of the mechanisms of these therapies can expand their applications, and how effective treatments must be thoroughly understood through careful longitudinal clinical studies and directed basic research. The chronicle of pho.tochemotherapy continues in the pages of the JID: In 1988 two papers from the PUVA cooperative group further document the long-term risks of non-melanoma skin cancer and causes of death in PUVA-treated patients [4,5].

The third Citation Classic is only 42nd in the list of the 200 most cited papers in the JID. This modest citation of 25 years ago was the first report of the effects of the protein which would be termed Epidermal Growth Factor, one of the prototype growth factors for which Stanley Cohen won the Nobel Prize for Medicine (with Rita Levi-Montalcini) in 1986. The importance of hormone-like growth factors in all aspects of biology has become increasingly evident in the 25 years since Stanley Cohen first reported the effect of EGF protein on epidermal thickness and keratinization in this classic paper in the JID. Growth factors are central to normal growth, development, and differentiation; in maintenance of homeostasis and repair of tissue damage; and probably in many disease states such as autoimmunity and cancer. The pages of the JID in its 50th Anniversary year are filled with papers on the varied biologic effects of growth factors and cytokines on the structure and function of the skin. This paper is a classic example of how simple experimental observations can be expanded to affect large segments of biology.

No single topic is better represented in the 200 most cited papers in the JID than the epidermal Langerhans cell. The second most cited paper is that by Michael Birbeck, Aodan Breathnach, and John Everall, which describes the characteristic cytoplasmic granule found in Langerhans cells, which are now universally known as Birbeck granules [6]. A number of papers in the late 1960s by Aodan Breathnach and colleagues [7] and by Klaus Wolff and Richard Winkelmann [8,9] further demonstrated the distribution and ATPase staining characteristics of Langerhans cells, and began to address the processing of exogenous proteins by these cells [10]. In the late 1970s, the functional role of epidermal Langerhans cells was examined by increasingly sophisticated ultrastructural techniques and by basic immunopathologic approaches. The result was an explosion of new information on the role of the Langerhans cell as an accessory cell or antigen-presenting cell in contact hypersensitivity, allogeneic reactivity, and graft rejection. From this Langerhans cell era there are a number of highly cited papers reporting major investigative discoveries: description of the analogous functions of Langerhans cells and macrophages by Georg Stingl, Stephen Katz, and their colleagues [11,12]; description of the inhibitory effects of ultraviolet radiation on Langerhans cell markers and function [13]; and the description by Inga Silberberg, Rudolph Baer, and Jeanette Thorbecke of the interaction of Langerhans cells and lymphocytes in contact hypersensitivity [14,15]. We have chosen to provide commentary on the landmark work of the investigators from New York University because the concept that Langerhans cells were functional components of the cutaneous immune system was viewed as revolutionary when it was proposed. It heralded a new period in immunodermatology. During the past 20 years, the role of the skin as an immunologic organ has so expanded, that we now recognize that the involvement of several different cell types, cytokines and growth factors, combine to produce a truly exciting field of investigation [16].

The ability to grow keratinocytes in cell culture under defined and variable conditions has made a wide spectrum of studies in molecular and cellular biology possible, and has facilitated important studies in immunodermatology, the chemistry of matrix proteins and growth factors, and keratinocyte differentiation. It has also provided the opportunity to study the effects of drugs on the epidermis directly, and to use cultured autologous and homologous epidermis as grafts for severe burns and ulcers. Three major epidermal keratinocyte culture techniques have been developed and widely employed: the fibroblast-feeder layer technique of James Rheinwald and Howard Green [17], the collagen gel method of Marvin Karasek [18], and the serum-free defined medium system of Steven Boyce and Richard Ham [19]. We have selected the technique of Marvin Karasek and his collaborators at Stanford for commentary, for this technique evolved through three highly cited papers in the top 200 published in the JID in 1966, 1971, and 1978 (number 136[19], number 87[20], and number 62[18]). The advances facilitated by all of these techniques in a short time have been remarkable. By 1983, the burst of investigation in basic and applied science with the use of cultured human keratinocytes was so great that a special supplemental issue of the JID was devoted to the topic: “Biolog y of the Keratinocyte in Vitro,” which were the proceedings of the 32nd Annual Symposium on the Biology of the Skin [19].

The sixth Citation Classic is an example of another very important feature of the JID: the review article. A number of highly cited reviews have provided clear perspectives on important advances in cutaneous biology,
such as “the Immunopathology of Pemphigus and Bullous Pemphigoid” (citation number 4 [20]), “DNA Damage and Repair in Light-Sensitive Human Skin Disease” (number 11 [21]), “Interaction Between Keratinocytes and Dendritic Cells” (number 29 [22]), “The Pathogenesis of Dermatitis Herpetiformis” (number 44 [23]), “Defects in the Biochemistry of Collagen in Disease of Connective Tissue” (number 64 [24]), “Animal and Human Collagenases” (number 67 [25]), “Factors Regulating Growth and Pigmentation of Melanoma Cells” (number 79 [26]), “Pathogenic Mechanisms of Drug-Induced Photosensitivity” (number 112 [27]), and “Subsets of Systemic Lupus Erythematosus” (number 181 [28]). For commentary we have selected the review by Ernest Beutner, Bob Jordon, and Tad Chorzelski [20], not just because it is the fourth most cited paper in the JID, but because of the impact of cutaneous immunofluorescence in the diagnosis, treatment, and scientific understanding of the bullous diseases. This is clearly one of the best examples of basic research changing clinical practice. Immunofluorescence allowed the clear separation of a number of confusing bullous diseases which could not always be diagnosed by clinical presentation or standard histopathology. The separation of pemphigoid from pemphigus and from dermatitis herpetiformis facilitated the development and evaluation of rational therapy, and the evaluation of distinct immunomechanisms in these diseases. These techniques are standard in all modern immunoder-matology laboratories, and have been expanded to allow separation and study of acquired epidermolysis bullosa, chronic bullous disease of childhood, and erythema multiforme. The contribution by Gerald Krueger in the chapter “Immunology/Inflammation of the Skin: a Fifty Year Perspective” in this issue more fully describes the progress in scientific investigations of immunoreactants in the pathogenesis of the bullous diseases.

These six Citation Classics provide other interesting perspectives on the development of investigation in cutaneous biology, beyond the simple story of laboratories, experiments, and discoveries. These commentaries show us how important new concepts may grow from simple observations, how important techniques are developed through perseverance, how large multi-center trials and teamwork can produce important therapeutic advances, and how revolutionary concepts eventually win acceptance. They also illustrate the human side of investigation: the value of medical students, residents, and junior faculty in important discoveries, the importance of human volunteers and patients in developing new techniques and treatments, and the importance of reviewers, editors, and established investigators in promoting the development of new and important concepts.

REFERENCES