

Commentary on Stanley Cohen and *Epidermal Growth Factor*

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When Stanley Cohen submitted his Preliminary and Short Report to the *Journal of Investigative Dermatology* in May, 1962 [1], he had no idea of the impact epithelial or epidermal growth factor (EGF) would have on biologic and medical sciences. The *JID* was not the first journal that Stanley chose to submit his short paper on EGF and epidermal keratinization. Reviewers for an unnamed journal he first selected rejected this paper. These reviewers concluded that the effects he observed were a fluke and simply due to using sick animals in the experiments. Fortunately for the *JID* and science his paper was accepted with one reviewer commenting that if the observations were true, Stanley Cohen would become very famous. The unnamed *JID* reviewer's observations were and are true, and Stanley Cohen is now famous because he was a co-winner of the 1986 Nobel Prize for Physiology of Medicine with Rita Levi-Montalcini.

In the decade preceding the *JID* paper Stanley Cohen had been working in collaboration with Drs. Levi-Montalcini and Viktor Hamburger at Washington University (1953–1957). This group was studying the growth of nerve cells, and in 1956 Stanley purified nerve growth factor from certain mouse tumors that Levi-Montalcini had shown caused dramatic growth of the nervous system in chick embryos [2]. In 1958 he found NGF-like activity in mouse salivary glands when he followed up on his studies showing that snake venom, modified salivary glands, was a rich source of NGF-like activity. After moving to Vanderbilt University in 1959 with his lifelong friend, Sidney Colowick, Stanley continued to work with mouse salivary gland extracts [3]. He observed that newborn mice injected with salivary gland extracts had precocious opening of their eyes and premature eruption of their incisors [1,3]. The histologic documentation of the effects of the injected salivary gland extracts on epidermal keratinization were thus the findings reported in the *JID* [1]. To Cohen, but not many others except the reviewer and Dr. Naomi Kanof, the Editor of the *JID* at the time, it seemed clear that “the opening of the eyelids of newborn mice was offering some kind of clue to the mystery of biological timing.”

Cohen devised an ingeniously simple method for isolating and purifying mouse EGF in relatively large quantities [4], which allowed him to determine its primary structure [5]. Thus, EGF became an attractive, biochemically defined, natural substance to study why mammalian cells grow and differentiate. EGF was found by Cohen and others to stimulate the growth of many different types of cells and to enhance a variety of biologic process [6–10]. Using radioactive EGF, Cohen and his co-workers determined the existence of specific EGF receptors that mediated all the known effects of EGF [6–11]. The EGF receptor was found by his group (Carpenter, King, Ushiro, and others [11–14]) to contain an EGF-stimulated

protein kinase of the type mediating effects of other hormones and cancer-inducing viruses [9,10,13,14].

His work played a major role in the subsequent discovery by other investigators of previously unknown cancer genes and growth factors [9,10,13–15]. These growth factor and oncogene studies are now beginning to enter the clinical arena in the areas of diagnosis and therapy. Although the scientific impact of EGF [and NGF] has been dazzling, the impact of growth factors on clinical medicine promise to be even more exciting as the clinical pharmacology of peptide hormones becomes better understood. EGF is important in understanding and perhaps treating skin diseases and corneal wounds [8,16]. However, alone or in combination with related growth factors such as alpha TGF, even more impressive clinical effects should be demonstrated in the next few years. Growth factors also may be important in the diagnosis and treatment of cancer as has been shown for alpha TGF and its role in the pathogenesis of a paraneoplastic syndrome, the Sign of Leser-Trelat [17]. In retrospect, one would not expect such a small paper to have such a large scientific impact, but truth does often come in small packages. I applaud both the reviewers and Dr. Kanof for their insight.

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