Comment

THE EPIDERMIS AND CYCLIC AMP

A hormone induces a rapid and profound change in the metabolic balance of its target organ. Early studies emphasized the extraordinarily low concentrations in which many hormones are effective. The fact that catecholamines and polypeptides are frequently unable to penetrate the surface of cells made this seem all the more remarkable. The mechanism of their action, which for many years remained a central problem of molecular biology, was finally resolved by the discovery of adenosine 3′,5′-monophosphate (cyclic AMP) in 1958 by Sutherland & Rall. It subsequently became apparent that cyclic AMP was the intracellular second messenger for those hormones that by themselves could not penetrate inside the cell.

An overall but abbreviated sequence of events is shown in Fig. 1. When activated by cyclic AMP, a cyclic AMP dependent protein kinase may phosphorylate many different proteins, both enzymatic and structural. In some cases this results in their activation, whereas in others the protein is converted to a biologically inactive form. Thus, co-ordinate control over several different pathways is accomplished. In addition, the amplification obtained by linking enzymic reactions in cascade is considerable; one may visualize how a cell could respond to a very few molecules of the external hormone (the 'first messenger'). The most comprehensive review of the general literature is the monograph of Robison, Butcher & Sutherland (1971), which includes a bibliography of over 1500 references to cyclic AMP. It is notable but not surprising that this literature deals with almost every mammalian tissue except epidermis.

Does the 'second messenger' system in fact operate in mammalian epidermis? Adenylate cyclase activity was first described in homogenates of whole guinea-pig skin (Mier & Urselmann, 1970a), but no hormonal stimulation could be demonstrated. Using a particulate fraction isolated from epidermis, Duell *et al.* (1971) and Marks & Rebien (1972a) were able to show some degree of stimulation by catecholamines, although this was still very small compared with other tissues. Intact epidermal cells, on the other hand, respond vigorously; for example, Powell, Duell & Voorhees (1971) found a three-fold increase in the cyclic AMP content of rat epidermis following exposure to isoproterenol, and Brønstad, Elgjo and Øye (1971) reported increases of more than ten-fold in the synthesis of cyclic AMP by whole hamster skin in response to adrenalin. Thus, it is now clear that this part, at least, of the system is functional.

The other two enzymes shown in Fig. 1 have now also been described in mammalian skin. The enzyme responsible for lowering cellular levels of cyclic AMP after hormonal stimulation has ceased, cyclic AMP phosphodiesterase, was examined in whole mouse skin (Mier & Urselmann, 1972) and found to have a K_m of 9×10^{-5} M and was inhibited by methyl xanthines. The high K_m cyclic AMP phosphodiesterase has been measured in both involved and uninvolved psoriasis epithelium and appears to be unaltered (Voorhees *et al.*, 1973a). The low K_m activity might be increased in the lesion in comparison to the uninvolved areas (Voorhees *et al.*, 1974a). Cyclic AMP dependent protein kinase has been investigated in whole human skin (Kumar, Tao & Solomon, 1971), in whole mouse skin (Mier & van den Hurk, 1972) and in human epidermis (Voorhees *et al.*, 1974b); the cutaneous enzyme seems very similar to those from other tissues. Although certain of these results pertain to whole skin, the preponderance of epidermal cells in such preparations and the demonstration of all the components of the cyclic AMP system in human epidermis (Voorhees *et al.*, 1974a) makes it
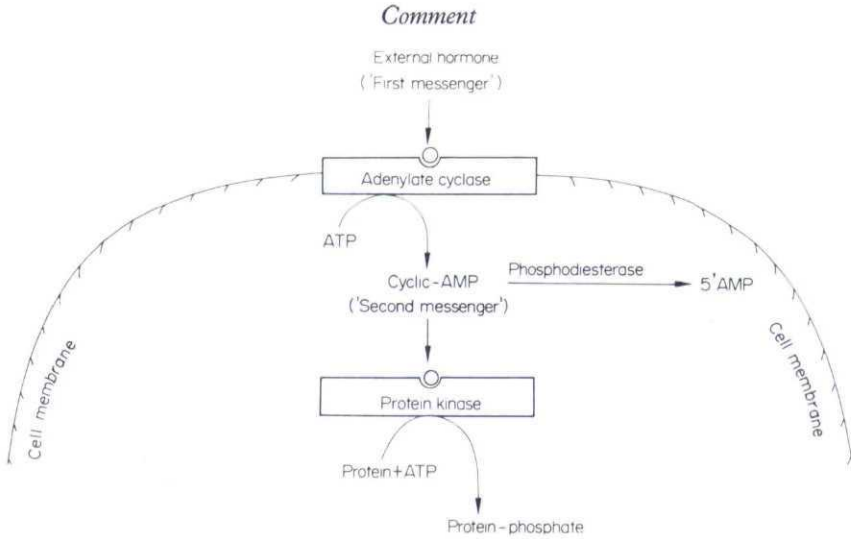
FIGURE I. The 'cyclic AMP cascade'. Both enzymatic and structural proteins may be phosphory-lated by the cyclic AMP-dependent protein kinase.

reasonable to conclude that epidermis is indeed equipped with a complete 'second messenger' system.

But what 'message' does this system carry? The activity of many internal tissues must be linked to the minute-to-minute needs of the body as a whole; since epidermis (as far as we know) does not secrete metabolites vital to other organs, it is more difficult to understand the need for such continuous hormonal supervision. What epidermis does provide, however, is a highly specialized barrier between the 'inside' and the 'outside'. An important parameter, therefore, is its thickness; one must presume the existence of a homeostatic device to balance the proliferative rate of the basal cells with the rate of desquamation from the surface. This homeostasis has been studied extensively by Bullough, who introduced the now familiar concept of the epidermal chalone (Bullough, 1962). In the course of this work it was established that catecholamines are powerful inhibitors of epidermal cell division.

Voorhees & Duell (1971) proposed that cyclic AMP mediates this catecholamine induced inhibition of proliferation. This hypothesis not only assigns a physiological function to the 'second messenger' in epidermis, but also explains (via the activation of glycogen synthetase and the inactivation of glycogen phosphorylase) (Fig. 2) why an accumulation of glycogen generally accompanies enhanced epidermal proliferation. In essence, the Voorhees–Duell hypothesis suggests that cyclic AMP is a major regulator (not necessarily the only one) of epidermal thickness and function. However, which hormone, if any, modulates intraepidermal cyclic AMP levels is unknown. The experimental support for this hypothesis is now considerable, and includes the following observations:

(1) *In vitro* studies have shown that cyclic AMP directly inhibits epidermal cell division in a dose-dependent manner (Marks & Rebien, 1972b; Voorhees, Duell & Kelsey, 1972). In fact, the four criteria of Robison *et al.* (1971) of a cyclic AMP mediated event (inhibition of epidermal cell division) have been met (Voorhees *et al.*, 1973a).

(2) In rapidly dividing epithelium, such as the psoriatic plaque, the level of cyclic AMP *in vivo* is decreased (Voorhees *et al.*, 1972).

(3) The degree of activation of phosphorylase (Mier & van den Hurk, 1974) has been reported as lower than normal in the psoriatic plaque.

(4) Wright *et al.* (1973) claim to have found a reduced rate of cyclic AMP synthesis in the psoriatic
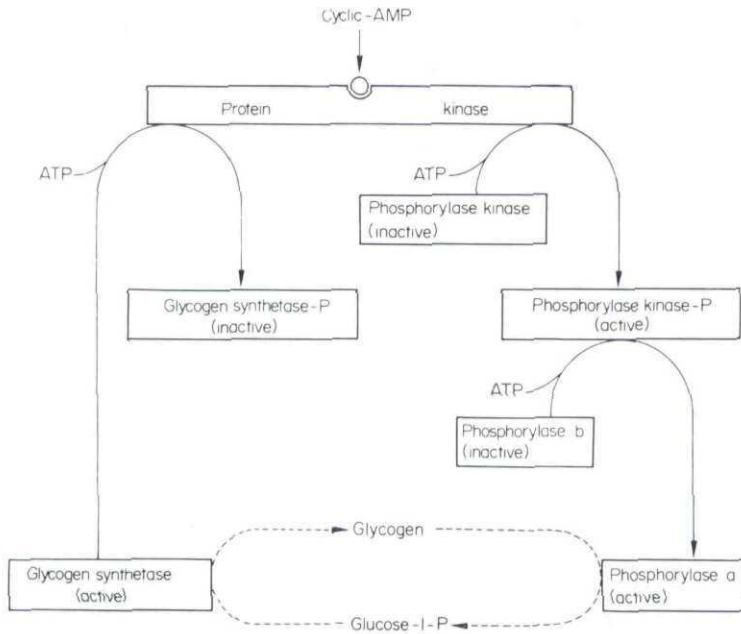
FIGURE 2. Control of glycogen metabolism via the activation of protein kinase. Most of the components of this pathway have now been demonstrated in epidermis.

plaque. This may be the case but requires further work and confirmation, as discussed by Voorhees *et al.* (1973a).

Can the pathogenesis of any of the familiar dermatoses be related to a defective 'second messenger' system ? So far two hypothesis have been offered. The earlier of these was the attempt by Szentivanyi (1968) to describe the clinical manifestations of atopy in such terms. Despite considerable circumstantial evidence in support of this idea, direct measurements of the three enzymes concerned (Fig. I) in four to six patients have failed to reveal any abnormality (Mier & Urselmann, 1970b; Holla *et al.*, 1972; Mier *et al.*, 1972). Although the enzyme activities are apparently normal *in vitro*, any final conclusions must await study of factors which may interfere with the function of these enzymes *in vivo* and the study of the adenylate cyclase receptors at the cell surface.

The more recent, and more promising, line of thought relates to psoriasis. The original suggestion of a defective cyclic AMP cascade in this disease was made by Voorhees & Duell (1971). As we have already pointed out, subsequent reports seem to support this notion that both the high proliferative rate and the accumulation of glycogen in the psoriatic lesion are due to a co-ordinate misregulation occasioned by reduced cyclic AMP levels. This provides an important new link in the pathogenic chain, but in no sense tells us the 'primary cause' of the disease. It would, of course, be tempting to equate the familial predisposition to psoriasis with an inherited abnormality of adenylate cyclase, cyclic AMP phosphodiesterase or the adenylate cyclase receptor. Current evidence, however, suggests that the disturbed cyclic AMP balance may be secondary to some other process—an inhibition of adenylate cyclase function or a stimulation of cyclic AMP phosphodiesterase *in vivo* without a major genetic defect in either enzyme (Voorhees *et al.*, 1973a).

In conclusion, it is perhaps pertinent to comment that the 10-year lag which has been customary before new 'scientific' thought is assimilated into dermatology seems at last to be diminishing. Skin is finally becoming an acceptable tissue for molecular biologists to investigate, and clinicians are becom-

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ing more aware that an understanding of many diseases in sufficient depth to lead to better therapy is possible only in molecular terms. If this trend continues, the following decade will be an exciting one for us all. Perhaps the most intriguing line of investigation in this area at the present time is the interrelation between cyclic AMP and cyclic GMP in epidermal physiology (Voorhees *et al.*, 1973a, 1973b; Voorhees *et al.*, 1974a, 1974b). The role of cyclic GMP in epidermal homeostasis will be the subject of a future commentary.

University of Michigan Medical School,   J.J.VOORHEES
Ann Arbor, Michigan,
U.S.A.

Department of Dermatology,   P.D.MIER
University of Nijmegen,
The Netherlands

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