

SUMMARY AND GENERAL CONSIDERATIONS

Sebaceous glands are known to man since time immemorial, but it has aroused the curiosity of scientists only in this century. The pioneering work of Rothman in the early part of this century (Rothman, 1954) led to further interest in this gland and gained impetus with the findings of Montagna (1974), Ebling (1974; 1977), Pochi and Strauss (1974).

Before 1950, most of the research on the sebaceous gland was focussed on its microscopic anatomy and the mechanism of secretion. The number of papers published since last three decades on the effects of hormones on sebaceous glands has been quite extensive and the progress in understanding sebaceous gland biology has been considerably rapid. Of these studies on the effects of hormones on sebaceous glands, that intended to give insight into their endogenous control, the number of papers pertaining to involvement of androgens surpass all the rest. Almost all the scientists engaged in this field have studied some aspects of the role this group of hormones play in the physiology of sebaceous glands. So many changes have occurred in the acquisition of new knowledge and new perspectives that some of the earlier statements have been proved to be incorrect. Even a cursory

perusal of the published proceedings of the symposia on the subject (see : Advances in biology of skin Vol.IV, The sebaceous glands. 1963, and Proceedings of the 22nd Symposium on the biology of skin-sebaceous glands and acne vulgaris-1974) highlights the importance of meaningful dialogue between morphologists, biochemists and clinicians in the elucidation of newer comprehensive frontiers of understanding. Interest in the physiology of sebaceous glands arose not only from scientific curiosity but also from the need to understand the pathology of seborrhea and acne, a common disease of human sebaceous glands, associated with attainment of adolescence.

Biologists long ago learned to take advantage of diversity of structural patterns of species to understand the functional aspects of a given structure by deduction. An advantage of easy isolation of rat preputial gland has helped to settle some vexing questions regarding mechanisms controlling sebaceous gland functions. Both hormonal and non-hormonal factors are important in the control of this modified sebaceous gland and the present investigation envisages to portray, on the basis of the observed findings, their relative involvement in the concerned mechanism that could be extrapolated in understanding the physiological attributes of the sebaceous glands.

To avoid abstruse discussion these factors are dealt with here under three separate headings viz., Mechanism of androgenic control, Mechanism of neural control and Role of adrenal gland in the physiology of the rat preputial gland.

Mechanism of androgenic control

As early as 1941, Hamilton reported an increase in skin oiliness and occurrence of acne in castrated males treated with testosterone. Androgenic stimulation of sebum production and secretion has been confirmed by several workers on the basis of their studies on sebaceous glands of varied mammalian species (Montagna and Kenyon, 1949; Hamilton and Montagna, 1950; Lapiere, 1953; Beaver, 1960; Martan, 1962; Glenn and Gray, 1965, Martan and Price, 1967; and 1972; Ebling, 1974 and 1977; Hsia and Voigt, 1974; Shuster and Thody, 1974). One of the factors implied in the glandular response to androgen is an increase in mitotic activity (Ebling, 1957a; b and 1963; Frost et al., 1973). It has also been reported that castration results in a significant decrease in glandular weight and size (Ebling, 1963). Profound influence of testicular androgen is also implied from the observation that there was a marked decrease in the activity of glucose-6-phosphate dehydrogenase (G-6-PDH) 24-hrs following castration (Chapter-1). Reduction in the

turnover of glucose through HMP-shunt, as evident from decreased activity of G-6-PDH would result in insufficient availability of pentose sugars for nucleic acid synthesis. Androgen deprivation was observed to cause a decrease in the activity of 'malic' enzyme in preputial glands (Chapter-1). Since, both these enzymes play an important role in the generation of NADPH_2 required for lipogenesis, they could be directly implicated in the androgenic regulation of sebaceous gland activity. It has also been observed that androgen deprivation causes the acid phosphatase activity of the rat preputial gland to fall (Chapter-6); this in turn could result in reduced rate of sebum secretion.

Its being eminently a holocrine gland (preputial gland); the rate of production of sebum in it directly reflects the overall biological activity of the sebaceous cells. Secretion of sebum is a function of synthetic potential, and is determined by the rate of replacement and maturation of cells. Present studies on the lipid content, levels of G-6-PDH, 'malic' enzyme and acid phosphatase activities (Chapter-1 and 6) and the study of Sansone et al. (1971) on lipogenesis (using labelled glucose) provide clues to the possible mechanism of androgenic control. It could be

suggested that androgenic control operates through its modulating effects at the enzymatic level. Changes in activities of these enzyme (G-6-PDH and 'malic' enzyme) would affect the synthetic potential, whereas changes in the activities of G-6-PDH and acid phosphatase would be reflected in variation in the time schedule of replacement of cells (mitosis) and cell maturation (secretion).

Histochemical studies on succinate dehydrogenase (SDH), malate dehydrogenase (MDH), β -hydroxy-butyrate dehydrogenase (BDH), lactate dehydrogenase (LDH) and α -glycerophosphate dehydrogenase (α -GPDH) reported in Chapter-2 contribute to the understanding of metabolic characteristics of the rat preputial gland. Grossly, metabolic patterns of the rat preputial glands disclosed in this thesis appear to be similar to those of sebaceous glands, which have been extensively reported and reviewed by Michael and Hoopes (1974) and Wheatley (1974). High α -GPDH activity in the preputial gland could be considered important for glycerogenesis to support triglyceride and wax syntheses which form the major part of the sebum. Malate cycle also appears to be operating at a higher rate as evident from the observed high MDH and 'malic' enzyme activities in the preputial gland. On comparison of the activities of dehydro-

genases in the gland of castrated rat with those of intact ones, it becomes readily evident that androgenic control is mediated by a generalized influence on wider spectrum of varied metabolic pathways also.

The study of histochemical distribution of hydroxysteroid dehydrogenases in the rat preputial gland (Chapter-3) revealed that the gland is not a passive respondent to the androgenic hormones but the hormones are subject to metabolic transformations within the glandular tissue under the catalytic influence of these enzymes. 17β - and 3β -hydroxysteroid dehydrogenases exhibited higher activities in the peripheral and differentiating cells as compared to the cells undergoing degeneration in the central parts of the acini. On the contrary, 3α -hydroxysteroid dehydrogenase activity was found to be localized more in the central parts of the acini of the rat preputial gland. Thus, this differential distribution pattern of hydroxysteroid dehydrogenases in the acini of the rat preputial gland is indicative of different microenvironments of different cell populations within the acini. Observed low activity of 17β -hydroxysteroid dehydrogenase, as compared to that of 3β -hydroxysteroid dehydrogenase, is in good agreement with biochemical findings of Hodgins and Hay (1973). Further, it has been shown in the

present report that, the activities of hydroxysteroid dehydrogenases decreased after castration which shows that hydroxysteroid dehydrogenases are highly sensitive to the circulating level of androgens.

Neural Control

Although there is a wealth of information on the hormonal control of sebum secretion, there is a dearth of substantive studies on neural control of the functions of sebaceous glands. As for hormonal control, this problem also has a history of about 3 decades only. However, the comparatively poor progress in this field leaves the question of neural control of sebum secretion at a tantalizing stage.

Twenty five years ago, a feed-back mechanism was generally accepted as the controlling force for sebaceous glands. This theory was for the first time challenged by Kligman and Shelly (1958) who after careful experimental work proposed that the sebaceous glands secrete continuously. The theory of feed-back mechanism of control of sebaceous gland secretion was rejected on the ground that neurohistologic studies yielded no evidence of secretory innervation for these glands. Even Montagna (1963) after studying acetylcholinesterase histochemically, showed that no acetylcholi-

nesterase positive fibers were present in the gland itself and he considered the innervation of the sebaceous gland to be fortuitous. Thus, the very question of innervation is itself disputable. There are, however, some reports in the literature dealing with the problem of innervation of the sebaceous glands (Rothman, 1954).

The present investigation employing anatomical, histological and histochemical methods - has clearly shown that the rat preputial gland, a sebaceous analogue, is richly innervated by adrenergic as well as cholinergic nerve fibers (Chapter-4). Both AChE positive and adrenergic fibers are found to traverse the connective tissue trabeculae located between the groups of acini and also in the connective tissue surrounding the major ducts. Adrenergic innervation was detected using fluorescence technique and was confirmed by reserpine and 6-hydroxydopamine treatment. It seems unlikely, at this stage, that the neural component could be attributed with any significant influence on the metabolism of the gland. However, as far as the rat preputial gland secretion is concerned, it has been convincingly shown that the expulsion of preformed sebum is under the control of α -adrenergic system (Chapter-5).

It would be tempting to extrapolate these results to

the cutaneous sebaceous glands; however, one has to be cautious before drawing inferences because there may be species specific differences; also that the rat preputial gland is a highly modified sebaceous gland. Nevertheless, at the outset it is worth mentioning here that recently the supporters of feed-back theory have come back (Archibald and Shuster, 1973) and have shown that when lipid is repeatedly removed from the rat skin there is an increased rate of sebum secretion which is a function of frequency of degreasing. Thus, the theory of neural control of sebum secretion requires serious consideration of these reports by those who are non-supporters of the theory.

Role of adrenal cortex and catecholamines

The adrenal gland produces a number of hormones, some of which are androgenic. Dehydroepiandrosterone, a hormone emanating from the adrenal cortex, has been shown to possess slight sebotrophic activity in castrated rats (Archibald and Shuster, 1969). The rat preputial gland depicted low 17 β -hydroxysteroid dehydrogenase activity and it could be suggested that the dehydroepiandrosterone could be converted to active androgen in the gland itself to some extent. It has also been shown that the removal of the adrenal gland in rat

produced decrease in sebum secretion (Thedy and Shuster, 1970a,b; 1971). Pochi et al. (1963) have shown that in a man with adrenocortical insufficiency, the level of sebum production rose sharply and markedly with physiologic replacement of hydrocortisone and 9 α -fluorohydrocortisone. Presently it has been reported in Chapters, 1. and 2 that activities of G-6-PDH and other dehydrogenases were lower in the preputial gland of adrenalectomized-castrated rats when compared with those in the glands of castrated rats. All these reports corroborate the view that the adrenal gland plays some important role in the physiology of the preputial gland and it could be suggested that such influence is exercised through modulation of certain enzymes involved in metabolic pathways.

Isoproterenol (IPR), a sympathomimetic agent (β -adrenergic agonist), has been shown to reduce acid phosphatase activity in the preputial glands of rats treated with this drug (Chapter-6). Histological study of the gland following administration of this drug revealed that it causes reduction in turnover of the acini of the rat preputial glands possibly through reduction in the frequency of mitoses as well as autolysis of mature cells. (Chapter-7). Since IPR is a β -adrenergic agonist it could be suggested that peripheral

levels of catecholamines in the body of normal rat may also play an important role in the physiology of the sebaceous gland. On the basis of this assumption, it could be said ^{that} a condition leading to an increase in the level of catecholamines would ultimately counteract the stimulating androgenic influence. The present observations may have significant implications in the pathology of the sebaceous gland and with further studies in this field it may lead to formulation of therapeutic measures. Further, the findings of Bullough and Laurence (1970) that a water soluble substance (possibly a chalone) from the skin which can be precipitated by ethanol and activated by adrenaline, inhibits mitotic activity in the sebaceous gland, substantiate the above mentioned contention.

It has been observed that IPR treatment of the rats caused drastic reduction in 17β -, 3β - and 3α -hydroxysteroid dehydrogenases in the rat preputial gland (Chapter-8), a condition identical with the activities of these enzymes in preputial glands of castrated rats. These results reflect a possible interference with the gland's capacity to effect androgen metabolism in the preputial gland of IPR treated rats.

It is difficult to suggest whether the effect of IPR and catecholamines is exhibited directly at the glandular level or through their effect on steroid metabolism in non-target organs like liver. The latter possibility can not be neglected because it has been reported that both IPR and catecholamines increase the activity of hydroxylase spectrum of the liver and thereby cause an increase in the biological inactivation of testosterone in this organ (Conney et al., 1973).

Though the precise mechanism of adrenergic (catecholaminergic) control of the sebaceous gland physiology is not known at this stage, these findings definitely open newer avenues for studies on factors controlling the physiology of sebaceous glands, for these studies need to be made not only to whet the appetite of researchers in basic sciences but also because they have far-reaching pathological and pharmacological implications.