SOME NEW CONSIDERATIONS ABOUT THE CHEMISTRY OF ACNE VULGARIS

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THE FOLLOWING discussion about the pathologic mechanism causing acne vulgaris is offered in all humility, on the basis of medical practice, clinical research and arm-chair philosophy. The theory to be presented is, to this observer, the most plausible key to the pathogenesis of acne vulgaris, and is the simplest explanation for all the known facts about the condition.

The prevailing dermatological thought about acne vulgaris is that it is a sebaceous gland dysfunction of the adolescent years, predicated upon an androgen plus progesterone/estrogen imbalance. Androgen is male sex hormone, estrogen and progesterone are female sex hormones. It is considered that androgens tend to predominate, and that the adrenal cortices are in some way involved. Secondary infection of the basic acne lesion—the blackhead or comedone—produces the pustules of acne.

At this point it is necessary to realise that repeatedly observed clinical and laboratory data about acne are factual; but some serious illogic is involved in the current explanatory theory of androgen/estrogen imbalance.

1. It is a fallacy to assume that, because events coincide chronologically, they are causally related. For example, the epiphyses of the long bones fuse during puberty, but that does not mean that epiphyseal union is a cause of the acne of adolescence. In like fashion, it is very questionable that, because androgens and estrogens come into play during adolescence, they therefore must cause acne.

2. It is erroneous to assume that factors that have an influence upon a situation must necessarily cause that situation. For example, bacterial infection can cause pustular lesions in acne, but that does not mean that bacterial infection causes acne. In like fashion, the androgens, progesterones, and estrogens that come into play during the teen years persist throughout a great part of mature life, when acne vulgaris is not generally present. These hormones influence the course of acne, but do not produce acne.

A study on the urinary excretion of 17 ketosteroids (a neutral hormone that represents androgen and adrenal cortical activity) showed no difference in values between acne and non-acne patients. In the same study, the 17 KS/estrogen ratios were the same in normal persons as in acne patients.[1]

It has been observed that administration of the androgen, testosterone, can produce an acneform eruption; however, even in boys 50 to 70 per cent of the body steroid output (that is measured by 17 KS excretion) comes

from the adrenal cortical hormones. Adrenosterone, the adrenal cortical androgen, is only very weakly androgenic, and only an abnormal variant of adrenosterone is secreted in adrenal virilising tumours, where acne results.[2] 17-Hydroxy progesterone, an intermediary product in the metabolism of adrenal cortical hormones, has marked androgenic effects.[3]

These evidences thus argue against androgens alone being etiologic in acne vulgaris.

3. It is customary to speak of an acneform eruption that follows the use of ACTH, cortisone and its derivatives. This acne is referred to as steroid acne ; and is a simple case of poor semantics. Estrogen, which is known to inhibit acne, is a steroid also, and has that same phenanthrene nucleus common to all steroids. A more apt name here would be acne due to adrenotropic and adrenal cortical hormones.

4. Another fallacy is the assumption that the androgen/estrogen ratio must be out of balance in acne vulgaris, because estrogen is antagonistic to androgen and because estrogen inhibits acne. It is necessary to look further to see what other hormones are antagonistic in effect to estrogen. A new field then appears, where estrogen is antagonistic to pituitary growth hormone, to gonadotropic hormones of the anterior pituitary, and where estrogen has other effects, such as the ability to stimulate adrenotropic hormone production.[2]

5. Negative evidence must be weighed with care. For example, to say that an object is not green, does not mean that the object is blue. It could be violet, yellow, or red also.

The effect of testosterone in producing acne has been supported by the observation that prepubertal castrates and eunuchoid males do not develop the skin condition. Other factors enter here. These abnormal individuals also do not develop beards, have altered body growth and hormone output, and do not present the usual emotional adaptation problems of adolescence.

6. Lest it still is a temptation to ascribe acne entirely to hormonal aberrations, it should be noted that other mammals—that have hormone systems—nevertheless do not have acne.[4]

When the current misconceptions are laid aside, then slightly more rigorous thinking may be indulged. To begin the development of a more rational theory, some fairly definite facts about sebaceous glands, adolescence and acne vulgaris must be reviewed.

The sebaceous glands, which are the site of acne, empty into the hair follicle, the whole being referred to as the pilosebaceous apparatus. Like other organs and systems, the sebaceous glands enlarge markedly in size during adolescence ; and the secretion of sebum has been found to be proportionate to the gland surface.[5] However, the sebum output falls to a stationary level between ages 20 to 25,[6] while the gland surface area remains the same. So another additional reason for the highly accelerated

sebum secretion of the 'teens must exist. It is thought that ordinarily sebum is produced at a relatively constant rate.[7]

The sebaceous gland empties into the hair follicle that is continuous with it. In acne, the hair follicle adjacent to the gland is filled with a horny plug—a hyperkeratotic or parakeratotic scale. Possibly, this may indicate pressure from the enlarged sebaceous gland on the contiguous epithelium, or it may be an independent process—perhaps of alteration of the hair follicle itself. Boys, at adolescence, develop beards—which could be a sufficient reason *sui generis* for the parakeratotic plug in the follicle.

Anatomically, the epithelial wall of the hair follicle just adjoining the sebaceous gland has a clearly distinguished stratum granulosum during early acne only.[8] The stratum granulosum is a transitional layer between non-cornified and cornified (horny) epithelium. This layer contains microscopically visible keratohyalin granules, so called because they swell in alkaline solution—like hyalin. The granules are thought to represent proteins or protein decomposition products.[9] Consequently, the hair follicle plug in acne is a manifestation of a change in protein metabolism.

The acne lesion has been observed to develop when the hair root in the involved follicle is in the telogen or resting phase of the hair growth cycle.[8] Interestingly enough, the resting phase of the hair cycle can be initiated or prolonged in mice by the administration of adrenal cortical steroids.[10]

The sebaceous glands themselves have no known nerve supply, but, rather, are suspected of being acted upon by endocrine secretions (the chemical output of the ductless glands). Since acne occurs in both boys and girls, it is obviously not entirely dependent on sex. A recognised observation is that there is a premenstrual aggravation of acne vulgaris, and this is ascribed by some to a decrease in estrogens (which inhibit acne) with resulting free play of the steroids of the adrenal cortex. Yet, the adrenal cortical steroids are secreted throughout a much longer part of life than puberty; and the degree to which these hormones mimic testosterone is not clear, although evidence exists for the androgenic effect of an adrenal degradation product, 17-hydroxy progesterone. The existence of a clinical picture of acne after ACTH, cortisone or derivative therapy is established.[11] Here, a paradox must be mentioned. Cortisone is used in treating the disease adreno-cortical virilism.[12] But both cortisone and the condition, adreno-cortical virilism, can produce a clinical picture of acne. Thus, there must be a third factor, a common denominator that will explain why acne results from both instances.

What else is definitely known? A quick review of the endocrinology of adolescence related to understanding acne is now in order.

The pituitary gland, located next to the brain, is the master gland of the body. However, supreme control of endocrine secretion resides in the

hypothalamus of the central nervous system. (To illustrate, before adolescence the central nervous system directs the pituitary to remain quiescent and not to produce sex gland stimulating hormones.) Once pituitary activity starts, it regulates the endocrine glands by a check and balance mechanism. The anterior portion of the pituitary gland puts forth so-called pituitary tropic hormones that stimulate the endocrine glands to secrete. The endocrine target glands in turn secrete characteristic hormones. If the target gland output is insufficient, there is a compensatory increase in pituitary tropic hormones as a stimulant ; if target gland secretion is excessive, there is a compensatory decrease in pituitary tropic hormone as a depressor.

The anterior lobe of the pituitary elaborates a series of hormones. The most significant ones for this thesis are

(*a*) pituitary growth hormone ;

(*b*) the adrenotropic hormones ;

(*c*) the gonadotropic hormones, which maintain the activity of the sex glands—the ovaries and testes.

In the female, the pituitary hormones are Follicle Stimulating Hormone (FSH), and Luteinising Hormone (LH).

In the male, the hormone paralleling FSH influences the male gonad, and the luteiniser acts predominantly on the connective tissue derivatives—*i.e.*, the interstitial cells of the testes. Also, the anterior pituitary puts forth

(*d*) a thyreotropic factor ; and

(*e*) a lactogenic factor.

Pituitary Growth Hormone (PGH) has a tremendous effect on the adolescent growth spurt. PGH is a protein, of molecular weight about 45,000 and of exact structure as yet undetermined. It acts directly on body structures rather than through a subsidiary endocrine gland. It has a profound relation to protein metabolism, and is a protoplasmic anabolic hormone—*i.e.*, it causes body or tissue growth (anabolism), as opposed to utilising food by breakdown for energy (catabolism). Young animals whose pituitary glands have been removed show decreased growth that cannot be corrected by replacement with target gland extracts (—*e.g.*, thyroid or adrenocortical hormones, or testosterone—which contributes to nitrogen or protein anabolism.) PGH promotes growth simply, and does not promote maturation. Probably, PGH has some relation to the pituitary sebaceous gland tropic factor that has been postulated[13]—since the sebaceous glands are body structures, not glands of internal secretion. PGH can cause increased serum alkaline phosphatase in experimental animals.[14] In man, tissue alkaline phosphatase is demonstrable in normal sweat glands and hair follicles, and also around the affected follicles in acne vulgaris.[15]

Estrogen can inhibit the growth promotion of PGH as well as inhibiting the gonadotropic secretion of the anterior pituitary. Estrogen also has the faculty of stimulating the output of adrenocorticotropic hormone (ACTH). ACTH is capable in turn of aggravating acne. Another estrogen effect is the hastening of skeletal maturation. Estrogen, used experimentally in acne therapy, can produce damage to the testicular tubules.

The adrenocorticotropic hormones of the anterior pituitary elicit the adrenal cortical secretion of (1) DOCA, which regulates water metabolism, (2) the adrenal SFN hormones, which govern sugar, fat, and nitrogen metabolism—cortisone and corticosterone. The adrenal SFN hormones accelerate nitrogen catabolism, and so are antagonistic in effect to PGH. They have been demonstrated to have some bearing on the metabolism of compounds with SH groups—thus perhaps some bearing on skin metabolism.[16] Another adrenal cortical hormone is (3) adrenosterone, which may be a partial degradation product of the SFN hormones.

The next area for consideration, and the particularly new aspect of the theory that is here presented, is the interplay between the sebaceous gland and the eccrine sweat gland.

Because acne vulgaris is more severe in the tropics, where sweating is increased, the clinical effect of decreased sweating in patients with acne was assayed.[17] A complex form of aluminium hydroxychloride* was tested on skin in a 20 per cent aqueous solution. Thirty-three patients, treated for periods up to six months, between August 1954 and August 1956, showed accelerated initial clearing and easy maintenance of the end result—a less oily, acne-free skin. They were contrasted with 33 control patients.

Laboratory investigators have observed that the rate of sebum spreading over a wet skin is of the order of at least 10^3 times the rate of flow and spread on a dry skin.[18] Conversely, variations in the level of ether-soluble substances (fats) in skin directly parallel the level of sweat delivery in the skin area.[19] Thus, an antiperspirant becomes a logical empirical sebaceous gland inhibitor.

In the pathogenesis of acne, then, the substantial increase in sebum during puberty may be attributed to increased sweating.

What are the causes of increased sweat production ? Normally, temperature is an important conditioning factor. Hyperidrosis has two distinct mechanisms. One is an abnormal increase in nerve impulses to the sweat gland—such as may occur in central nervous system disorders ; and the other is emotional stimuli—such as fear, anger, etc.[20] Even straight mental problems—*e.g.*, arithmetic—have been shown able to evoke sweat. The disturbance in all these cases produces the liberation of excessive amounts of acetylcholine, and subsequent excessive perspiration.

* Astringen, supplied through the courtesy of Robinson, Wagner Co., New York City.

The thought now occurs that the known emotional problems and emotional flux of puberty, the pubertal crisis, can evoke sweating which in turn can greatly increase the amount of sebum flow.

As is generally accepted (and is the subject of a study by the author now with the New York City Board of Health and Board of Education), acne does not occur in all teenagers. Acne vulgaris is, then, not a universal response, or adaptation. At this date, only a suspicion can be recorded that it may have to do with unusually severe problems in adaptation.

Now, the basic pattern of development of the comedone of acne vulgaris can be postulated as follows :

A. The marked physical growth of puberty is accomplished largely via the Pituitary Growth Hormone. It, or a parallel hormone, causes simple increase in size of the sebaceous gland, with a directly proportional increase in sebum output.

   The PGH, which regulates protein anabolism, may relate again to the formation of the horny plug in the hair follicle, since this is a protein product.

B. The stress or alarm reaction consists of increased nerve impulses to the hypothalamus, which in turn stimulates the anterior pituitary to put forth ACTH, which in turn again causes increased adrenocortical hormone secretions.

   The adrenocortical SFN hormones—which cause nitrogen metabolism or breakdown—can foster the development of acne, apparently by an effect on the hair follicle hyperkeratotic or parakeratotic scale. Corticosterone and cortisone can induce the resting phase in the hair cycle—at which time the acne lesion appears.

   The increased 17 ketosteroid urinary output at puberty may reflect stimulation of the entire adrenal cortex rather than androgenic steroids only.

C. Alarm or stress—the emotional stresses of puberty—produce increased nerve impulses (anatomically sympathetic ; pharmacologically parasympathetic) to the sweat glands, which in turn produce a tremendously increased amount of sebaceous gland secretion. Thus the great increase in sebaceous material behind the narrow plugged follicular orifice gives rise to the comedone.

   (A whole series of secondary infections, and bacterial allergic phenomena must be considered in the evolution of acne pustule.) As the stresses of adolescence subside, the tendency for comedone formation abates spontaneously.

The decisive reasons for acne vulgaris appear to be the adaptations unique to puberty. As these adaptations are inevitable, and culturally desirable, the treatment of acne vulgaris still remains in the exclusive sphere of dermatology.

Many further studies of corroboration of the presented theory will be required. Several among these are :

(*a*) the effect of climate on acne (theoretically, in cold climates where sweating is minimal, there should be less acne) ;

(*b*) a close study of the psychologic adjustments of severe acne patients, as opposed to clear skinned adolescents ;

(*c*) the role of adrenocortical steroids in producing beard growth, in affecting the hair cycle, and in causing follicular plugging ;

(*d*) the value of cultural conditioning at puberty, as a cause for acne, must be examined by checking the acne incidence in entirely isolated cultures—if any such remain ;[22]

(*e*) the effect of catabolic agents in preventing or lessening follicular epithelial hyperkeratoses ;

(*f*) a check to see whether hypopituitary dwarfs are free of acne and whether giants and adolescents suffering from hyperpituitarism have a greater incidence of acne.[23]

(*g*) greater attention to the pharmacologic inhibitors of perspiration—both topical and parenteral—in the adjuvant treatment of acne vulgaris.

SUMMARY

A new concept of the pathogenesis of acne vulgaris has been thus presented, after stripping away misconceptions that is consonant with the known facts about acne, and that should prove a valuable instrument in furthering the understanding and proper therapy of the condition. The basic new consideration is that acne vulgaris is a disease of adaptation, and is, in the light of understanding in 1957, inevitable in a certain percentage of adolescents.

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