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Estrogen therapy in acne vulgaris

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ESTROGEN THERAPY IN ACNE VULGARIS

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I Introduction

Acne vulgaris is a disfiguring disease which though rarely considered to be of great consequence by those not so plagued, is indeed an unhappy scourge to those afflicted. Its end stages following chronic infection of the inflammatory lesions, lead to scarring and permanent disfigurement It is particularly deplorable that this disease involves the skin of the face of those who must at the same time face so many other problems -- the adolescent. Thus while the patient is finding life in general an emotionally undetermined element, he finds that he must advertise that he or she is different.

Defined as a chronic inflammatory disease of the sebaceous glands, characterized by comedones, papules, pustules and scars, the disease is almost limited to the adolescent age group,Tobias(1). In fact it is, to a greater or lesser degree, so common a complaint to this age group as to be considered almost physiologic. Pick(2) points out that the age incidence of acne has been recognized in the colloguial language in Bavaria; the typical comedones and papules being known as "chastity bumps". Bruno Bloch(3) in an unselected series of 2136 school children, ages 6 to 19, found that 59.6% of the girls and 68.5% of the

boys had at least some degree of acne; and further that 96.6% of the 17 year old boys and 99.5% of the 18 year old girls had acneic lesions.

This disease is thus an important, though not life-threatening, matter to a large segment of the population; and its therapy is considered by this student to be a subject worthy of consideration in a senior thesis. As is the case with nearly all dermatoses, therapy is difficult to evaluate since remissions and exacerbations are the rule. As is true in regard to all other medical literature, much has been written in regard to the therapy of acne which has little basis either clinically or experimentally. In this paper there has been an attempt to investigate the recent literature regarding the therapy of acne vulgaris with orally administered estrogens.

II Clinical Observations Suggesting Endocrine Etiology

Since acne is associated with puberty, the time during which the sexual glands are being awakened to activity, it is not surprising that those investigating the possible etiology of acne, should link the activity of the gonads and/or the pituitary in some manner with the occurrence of acne vulgaris. Pick(2) and Hollander(4) in 1921 were among the first to publish reports of this correlation and advance the theory that hormonal imbalance might play a major part in the etiology of acne. Hollander believed that the imbalance of function was one of thyroid activity secondary to gonad activity. Schamberg(5) during the same year pointed out as a general experience of many dermatologists, the observance that many female patients with acne have menstrual exacerbations of their acne. Schamberg thus believed the inference justified that " an internal secretion of the sex glands or some other internal secretion energized by the gonads is an etiologic factor of importance." Mumford(6) pointed out that 40% of a series of 100 cases of acne in females either had menstrual irregularities at the onset of acne or developed these irregularities after the onset of the disease.

Clinically it has been noted that not only is there an increased incidence of the disease during adolescence, but that it is almost non-existant during childhood. The

disease usually disappears as the physiology of the patient reaches an adult status, Lawrence (7). On the other hand, acne often persists for years in men and women who suffer hypogonadism. Pregnancy frequently is beneficial to the skin of acneic women; though at times it aggrevates the condition. The lesions of acne, frequently are found in female patients with masculinizing tumors; their disappearance after the removal of the tumor suggests an association between acne and disturbed androgen-estrogen balance. Eunuchoid and castrated males do not develop acne, Payne(8). Sulzberger (9d) observed the development of acneform eruptions following prolonged ACTH therapy. Acneform lesions are common menopausal symptoms.

Goldzieher(10) in citing evidence in favor of the endocrine pathogenesis of acne observes that treatment with testosterone in either the male or female patient is likely to antecede the eruption of acneform lesions; and that these eruptions are considered a part of the generally recognized "adrenogenital syndrome" in both sexes.

The clinical observations made by these investigators and others prior to 1940, appeared to support the hypothesis (endocrine pathogenesis of acne) to such a degree as to be indisputable. Thus Sulzbergher(9a) in 1940, wrote, "Acne vulgaris is undoubtedly the result of influences directly or indirectly attributable to adolescence

and, more precisely,to the development of the gonads and their secretions. The basis of the acne process may be directly attributable to the local effects of the sex hormones on the pilosebaceous apparatus, in the sense that there may be either a faulty ratio or form of hormonal supply, or there may be a lack of local adjustment, or a faulty or excessive local response on the part of the pilosebaceous apparatus to normal hormonal supply or both these mechanisms may be conserned. Whatever the exact nature of the hormonal aberration, acne vulgaris is due primarily to hormonal effects. Therefore fundamental causal treatment must consist of endocrinologic management".

III Laboratory and Experimental Evidence Suggesting Endocrine Etiology

Hamilton(11) has shown that some eunuchs and castrated males, prepubertal youths, and ovarectomized women develop acne when given testosterone propionate; and that these acneform lesions disappeared when the dosage of the male hormone was discontinued. His work indicated however that certain factors of susceptibility or readiness of the organ of response, ie of the local sensitivity of the skin and pilosebaceous apparatus, were operating since even with high doses of testosterone, not all subjects developed acne lesions.

This response of hyperplasia of the pilosebaceous apparatus to testosterone as well as a hypersecretion of the glands has been noted by Geist(12), Selye(13), Rony and Zakron(14), and Butcher and Parnell(15). The inhibitory effect upon the secretion of the sebaceous glands and the involution of the pilosebaceous apparatus following the administration of estrogens has been reported, Hooker, C.W. and Pfeiffer,C.A.(16),Geist(12),Selye(13), and Barber(17). Similar changes have been reported by animal experimentation with rabbits, Reiss(18) and dogs, Mulligan(19).

Accordingly there have been numerous studies of the blood and urine of patients with acne, which have attempted to show either a decrease in the amount of estrogens or

increase in the amount of androgenic substances. Rosenthal and Kurzok(20) were unable to detect any urinary estrogens in the urine of 34 female acne patients. Mice were used in their bioassays. Wile, Snow, and Bradbury(21) in their study of the urinary excretion of estrogens in 20 normal and 12 acneic female patients of similar age group(15-21) found a moderate increase in urinary excretion of androgens (capon bio-assay) and moderate decrease ,3.6 rat units, in urinary estrogens. Lawrence and Werthessen(22) in a similar study in 8 Normal and 8 acneic women during the 16th to the 20th day of their cycle (presumed highest hormone excretion) determined that the ratio of androgens/ estrogens in the normal female was 2.46 and 6.67 in the acneic individual. Though his series was small, the probability of such a difference being due to chance alone was but 1 in 100. First(23) showed that the normal female excretes about 75% as much androgens as the normal male, and believed that such a bioassay of 17 ketosteroids served as an index of adrenal function in the female. Gallagher(24) demonstrated pronounced fluctuation in daily urinary excretion of androgens and estrogens in normal males and females. He was not able to discover any definite evidence of a monthly cycle in the excretion of either androgens or estrogens in the male; whereas in the normal female the excretion of estrogens in characteristically low during menstrual flow and normally increases to high levels during the intermenstruum.

Rosenthal and Neustaedter(25) using mice for bio-assay of blood estrogens found a marked decrease in the amount of circulating estrogen in 93% of a series of 29 acneic females and concluded that a deficient secretion of estrogen was a factor in the production of acneform lesions. Cornbleet and Barnes(26) using chick's comb bio-assay of chloroform extracted androgens found that urinary androgens in acne patients, male or female, fell in the lower portion of the normal values. Normal daily excretion of androgen in the average female was found to be 3 units and 4 units in the normal male. In acneic females the urinary androgens by this method was 1.9 u and 2.0 u in the acneic male. White and Peterson(27) in the determination of the 24 hour urinary 17 keto-steroids in 26 young men with acne found the average daily excretion to be 13.1 mgm/24 hrs, or a deviation of 30% or less(within normal limits) from the normal value. Thus they could find no evidence to substantiate the concept that acne vulgaris is related to an excess of androgenic hormone; since their series of acne patients excreted quantities of 17 ketosteroids comparable to the quantities excreted by normal young men of similar age.

Nathanson and Towne(28) and Way,and Andrews(29) calculated that blood estrogen levels in normal menstruating women was highest from about the 10th to the 22nd day post menstrually. McCarthy and Hunter (30) found in a

series of 72 acne patients(12 males) that 41% of the males showed a dysfunction of either the pituitary gland ,as shown by bio-assay for gonadotrophins, or gonads,by bioassay for estrogens, or both; while there was a similar deficiency in 78% of the women. The lowest levels of estrogen are reached a few days pre-menstrually, while a second low level is noted a few days post menstrually; therefore exacerbations of acne tend to occur at precisely those times when the androgen/estrogen ration tends to be highest(assuming androgens are fairly constant). Progesterone is liberated from the active corpus luteum at about the midperiod intermenstrually and is found in the blood immediately after ovulation. The blood level of progesterone increases until the premenstrual phrase and then disappears completely 24-48 hrs after the onset of flow. Since studies indicate the progesterone is slightly androgenic, menstrual exacerbations can be reasonably explained,Goldzieher(10).

Thus while it is generally accepted that endocrine imbalance must be accepted as one of the etiological factors of acne vulgaris, the exact nature and origin of the abnormality is as yet still open to some question. The pathological physiology will be discussed later.

IV Other Etiologic Factors

One of the characteristics of Acne Vulgaris which makes its therapy complex is th multiplicity of its etiology. Commonly listed predisposing factors are age, puberty and adolescence, constipation, menstrual disorders, focal infections, seborrhea of the scalp and specific hypersensitivity to certain foods, viz, chocolate and milk, Tobias(1). Stokes(31) mentions in addition to these the possibility of a familial or hereditary tendency, the hypothetical double infection theory(a yeast and a Staphylococcus), the hyperactivity of the sebaceous glands, and the allergic element included in infections and contact allergies as well as those which are dietary. In addition, in his list of thirteen possible factors he lists the psychoneuro-genic component, the iodide and bromide factor, fatigue, and contact inoculation. Baird(32) stressed the importance of the abnormal sebaceous secretions of the pilosebaceous apparatus and the low resistance of the patient to bacterial infections, with the local hypersensitivity to the presence of bacteria and, or abnormal sebum.

Stokes(31) and Way(29) observed that the retention of salt and water following the administration of the adrenocorticoids, estrogen or testosterone might be important causitive factors and of particular significance in acne

seen near the time of menses. Andrews(33) assumes that in pustular, nodular and cystic cases the patients are usually sensitized to the staphylococcus; foci of infection persisting and often appearing to be the sole factor leading to the continuation of the disease. The teeth were involved in 64% of his series having foci of infection; tonsils in 28%, and sinuses in only 3%. Payne(8) indicated the possible role of vitamin deficiency as an etiologic factor. Hypothyroidism of a clinical or sub-clinical level has long been considered to be of moderate importance in the etiology of acne, Kalz(34),Andrews(33) and Payne(8).

V Pathologic Physiology and Pathogenesis

Acne vulgaris is a chronic inflammatory disease of the sebaceous glands in which hypertrophy of the glands, exudation of sebum and pus, with inflammatory changes in the follicles and adjacent reticular tissue of the corium give origin to the typical skin lesions of papules, pustules, and hypertrophic nodules. Sympathetic stimulation of the pilosebaceous apparatus either directly or by sympatheticomimetic drugs, ie adrenalin or posterior pituitrin results in decreased secretion of the sebaceous glands, constriction of capillaries and contration of the erector papilli muscles -- thus the skin is dry, pale and roughened with"goose flesh". On the otherhand when there is vagal stimulation by parasympatheticomimetic substances, ie gonadotropic hormones or the adrenocortico steroids, there is a resultant increased secretion of the glands, dilation of capillaries and relaxation of the erector papilli muscles. This stimulation (perhaps through the thalmus) results in a smooth, moist, oily skin which is flushed and like acneic skin except for the papules, pustules, etc, Nyvall(35). In severe cases the perifolliculitis and endofolliculitis of the lanugo hair follicles may progress to central necrosis. Infection leads to the ultimate production of cysts or abcesses.

It has been stated that the staphylococcus and acne bacillus play a secondary role in the production of acne lesions, Tobias(1). The exact pathogenesis is obscure, but it has been suggested that the fatty secretions of the follicle may be split by bacteria into choline and other end products which are irritating and thus lead to the typical hyperkeratosis. Sulzberger(9b&c) proposed that the delivery of the secretions of the sebaceous glands to the surface of the skin was determined by such factors as the patency of the terminal segment of the hair follicle and the enclosed hair shaft, the size of the opening of the follicle at the skin surface, the viscosity of the sebum, and the viscosity, emulsification, movement and removal of the layers of secretions and cells deposited at the follicular opening on the skin surface.

Butcher& Parnell(15) noted increased vascularity and activity of the sebaceous glands, with an increased amount of sebum excreted to the skin surface after gonadotropic hormone stimulation. Sulzberger(9b&c), Novy(36), and Fox(37) stated that the first step in comedo formation is the irritation of epithelium at the follicular mouth resulting in hyperkeratosis and narrowing of the follicular ofifice. Swelling of the keratin leading to the formation of a sebaceous and horny plug occluding the follicle and the hypersecretion or faulty secretion of the simultaneously stimulated and irritated gland, results in the formation

of the comedo or blackhead, Novy(36) and Fox(37). Comedo formation is thus probably due to hormonal stimulation leading to quantitative or qualitative functional and or anatomic changes in the pilosebaceous apparatus resultant in increased activity of the sebaceous gland and plugging of follicular orifices with epithelial hypertrophy, horny overgrowth and horny swelling, Sulzberger(9b).

Once the comedo is formed, mechanical pressure of the contents and stagnation or chemical changes in the trapped sebum result in secondary inflammatory changes, the mass here acting as a foreign body. These changes may reduce the resistance of the perifollicular tissues to infection; thus proceed to the formation of Pustules, Tobias(1),Sulzberger(9). "The degree of scarring following natural or therapeutic cure depends upon the extent, the duration and the depth of the infection and the specific reactivity of the tissues", Tobias (1)

VI Difficulties Encountered In Clinical Case Studies

The difficulties encountered in obtaining accurate results from a clinical study are perhaps so obvious as to obviate their numbering. The patients who are most resistant to therapy, or the neurotic are those who tend to seek help from the specialist. Kalz(34) has pointed out that a thorough follow up and use of case holding techniques, such as those used in the control of venereal disease, is impossible both in hospital and private clientele. Simultaneous use of external, dietary, and material therapeutic methods is often unavoidable since it is impossible to enforce strict dietary regimens.

The classification of the extent and type of lesions present is difficult to standardize; thus the reproduction of results by various investigators is difficult to obtain. The variance in individual response from time to time, and from individual to individual has already been indicated, Goldzieher(10). Payne(8) has noted that the skin sensitivity to estrogens varies tremendously in different individuals and at different ages. The female skin is more sensitive to androgens than that of a male, and a youth's skin is markedly more sensitive than that of a virile adult.

Evaluation of therapy is particularly difficult in a disease such as Acne Vulgaris, which has such a multiplicity of etiologic factors, such seasonal variations, and which is characterized by spontaneous remissions.C

Controlled studies are extremely difficult to plan, and much of what has been written concerns work for which no control study was attempted. Evaluation of therapy resultant from reading the literature is thus difficult to say the least.

VII General Measures in Therapy

While endocrine therapy for acne vulgaris has been attempted for nearly two decades, the results have been disappointingly confusing. This type of therapy therefore must be considered as radical in most instances. Following a review of the literature, the student was impressed that this was the majority opinion; even those writers who are most enthusiastic concerning endocrine therapy attempt at least some of the more conservative forms of therapy prior to its use.

Since this paper deals with the therapy for acne, and estrogen therapy in particular, it is thought that the general measures of therapy should at least be mentioned.

The hygiene of the skin must be meticulously managed with thourough washing with warm water and soap at bedtime. Comedones may then be expressed(after proper demonstration) and local applications applied. Local applications are aimed at correcting the overactivity of the sebaceous glands by astringents and anti-seborrheic agents or toward exfoliation to overcome the hyperkeratosis. Superfatted

soaps may be used on dry or delicate skins. The local applications meeting these needs are as manifold as the practioners using them. Seborrheic dermatitis of the scalp must ofcourse be controlled as mentioned by Stokes(31).

The excretion of irritants or allergans into follicles is controlled by diet and the elimination of foci of infection as well as culpable drugs.

Secondary infection is combated both locally and systemically by antiseptics and antibiotics. Andrews(33) suggests the use of sulfonamides or in those cases of resistant cystic acne, aureomycin, terramycin or dehydrostreptomycin. Aureomycin and Terramycin have been given in doses of 1 Gram daily for several months, and some cases of severe nodular and cystic acne have been cured on sulfa and antibiotic therapy alone. Evacuation of cystic and chronic lesions by expression,hot compresses, or surgery often hastens the involution of such areas.

Overactivity of the sebaceous glands, faulty keratinization and clogging of the sebaceous orifices with accumulated excess keratin may be counteracted by large doses of Vitamin A(50,000 u bid) and radiation therapy(Roentgen rays,& Grenz rays). Peeling and Drying may be induced by such physical measures as ultra-violet rays, scrubbing, and heliotherapy, as well as by the use of exfolliating agents previously mentioned. In extreme cases, Andrews(33) suggests the use of Carbon Dioxide slush or surgical scarification. X-ray therapy has been used for such a long time and with such success that it may no longer truly be considered

radical therapy. While its use should be restricted to resistant types, when properly used it has resulted in cures in about 90% of the cases, Tobias(1). It has its greatest value in those cases with oily skins and pustular or cystic lesions. Ten to Twenty percent of the cases require follow-up treatment after a year or more.

VIII Indications for Hormonal Therapy

As has been indicated, endorcrine therapy for acne has not met with universal approval, but those who use it consider certain types of patients better candidates for the therapy than others. Sulzberger(9d) states that endocrine therapy is indicated principally in women whose exacerbations of acne are clearly related to the menstrual period. Most writers, ie Becker(38) and Ayers(39), agree that endocrine therapy has best results in women, though by no means limit this form of therapy to treatment of the female.

IX Contraindications For Endocrine Therapy.

The sudden appearance of acneform lesions in the female should, of course, demand an immediate complete work-up to rule out the possible presence of a masculinizing tumor.

Grollman,A(40) states,in regard to endocrine therapy, "no toxic effects when used in reasonable dosages ...the steroidal hormones, estrogens, progesterone, and testosterone, when administered in large doses, over prolonged periods, may exert toxic effects , in addition to such harmful effects as may follow physiologic actions." Kimbrough, R. A. (41) mentions the carcinogenic effect of estrogen, and though, he agrees that laboratory experimental findings in animals are not applicable to man directly, they suggest that the use of estrogens is curtailed in the treatment of acne in so-called "cancer families" and in females over 40 years of age. Sulzberger, M. B. (9-41) suggests that hormonal therapy be avoided in patients under 18 years of age, unless exceptional circumstances appear to indicate its necessity. If other measures prove of little value, he does not hesitate to use endocrine therapy in this young age group.

On the other hand, Payne (8) indicated that endocrine therapy is highly effective with few untoward reactions, for acne in girls who have not reached maturity and in most cyclic exacerbations. He indicates

however, that occasionally, women with low ovarian function, tollerate exogenous estrogens poorly; thus it is important to start therapy with very small initial doses and to increase dosage slowly. In the sensitive person, symptoms of transient vulvar and breast swelling with discomfort and headache, persist for several days if the dosage has been too high. Other symptoms of nausea, vomiting, low abdominal cramps, metrorrhagia, increased libido in the unmarried female, and pigmentation of the nipples may occur. The resultant increased secretion of the vaginal glands, may cause an irritating vaginal discharge, or even a vaginitis or vulvitis. The administration of exogenous estrogens may aggrevate endometritis, chronic cystic mastitis and thus, is contraindicated in these conditions, or in the presence of cervical or endometrial polyps, fibroids, and most ovarian cysts. It is, of course, contraindicated in the female with suspected malignancy of the genital organs or breasts.

Males tolerate endocrine therapy well,developing transient symptoms of breast pain and engorgement with overdosage. Permanent gynecomastia is most likely to occur in the hypogonadal patient with a gynecomastic tendency. Thus, any tendency toward gynecomastia is a contraindication to endocrine therapy for acne. Becker (38) indicates that, though estrogens are thought to inhibit spermatogenesis, in doses of 0.1-0.2mg./day

for 4 months, estrogens markedly increased the sperm count in 56% of persons who were previously infertile; decreased the count in 14% and produced no change in 30%.

X Endocrine Therapy Using Oral Estrogens

During the past two decades, all of the gonadotrophic and gonadal hormones have been administered orally, systemically and topically in therapeutic attempts to alleviate Acne Vulgaris. Hormonal therapy for acne is, as yet in a state of flux and no satisfactory form of hormonal therapy has yet been definitely established. The literature is extensive and confusing; a part of the confusion has arisen as a result of those difficulties previously recorded in this paper (VI). Another factor leading to variation in therapeutic results, no doubt arises from qualitative or quantitative differences in the endocrine substances used in these investigations, recently and in the past. In an attempt to obviate, at least a portion of this confusion, the discussion in this part of the paper will be limited to that literature reporting the use of Estrogens by the oral route during the past seven years. That the situation regarding endocrine therapy for acne has always been confusing, it may be pointed out by Sulzberger (9-d). In spite of his own personal enthusiastic predictions regarding the future of such therapeutic attempts in 1940 (9-a), he stated that the situation was, in truth, unchanged eleven years later, in 1951.

In a paper in 1947, Goldzieher (10) stated that in treating acne in the female, anti-androgenic therapy in the form of orally administered estrogens seemed successful. He gave 0.05 to 0.1 mg. of stilbesterol, estinyl estradiol or premarin, daily during the second half of the cycle, beginning with the presumptive date of ovulation upon the first sign of a new skin lesion. Medication was continued until the onset of menstruation. Goldzieher believed that it was safer to treat acne in the male with topical estrogens. No statistical data was given though it was stated that there was considerable reduction in the number and severity of eruptions.

Goeckerman, W. H. (12), in a review of patients treated with estrogens over an 8 year period, reported "benefit" in all but one of a selected series of 26 female patients. He employed oral estrone and synthetic preparations in the form of estradiaol and diethylstilbestrol. The dosage except in rare cases, was small initially, but continuous. Patients were never allowed to become uncomfortable; at the first appearance of some abnormal response, the dosage was reduced immediately or temporarily discontinued. Dosage was adjusted to requirements, as judged clinically. An attempt at a control was made through treating male patients, first with testosterone, and when this proved unsuccessful, the therapy was switched to Vitamin A.

Andrews, G. C. (33) in a series of 384 patients, of which 341 had received estrogens in some manner in a combined therapy, reported 23% (90)pt. cured and 71% (276) improved. Treatment in simple cases, uncomplicated by pustular or nodular lesions, consisted of Vitamin A, general orthodox, conservative means of therapy, and estrogens, chiefly as enteric coated tablets of diethylstilbesterol in single daily doses of 0.25 mg.; rarely changed to 0.1 mg. or 0.5 mg. On occasion the estrogens were administered in a capsule containing 0.25 mg. estrogen, powdered extract of cascara, and desicated thyroid. When menstrual cycles, which had previously been regular,became irregular, dosage around the menstrual cycle was adjusted by large parental doses (10,000 r.u.) of estradiol benzoate. Other means of adjustment consisted of a dose of 20 to 25 mg. of progesterone, given in anticipation of the menses. Of the 341 patients receiving estrogens, 154 of them received the hormone for 3 months or less. An attempt at a control study was made by the selection of 253 pt. records of the 1287 records of patients treated with x-ray 3 years previously. All had received more that 600 r to each side of the face, and not more than 1400. Of the 253 patients, 60% were entirely cleared or improved, while 20% had cleared but had recurrences.

Sulzberger (9-41) used doses of 0.5 mg. and 0.625 mg., bid, of diethylstilbestrol or premarin, respectively. When menstrual irregularity precluded the inauguration of the schedule of premenstrual administration, the endocrine was given for 10 days beginning with the first day of flow. In exceedingly severe cases, 0.5 mg. diethylstilbestrol, bid, uninterruptedly for one or more months till the patient clinically improved or noted enlargement of the breasts or loss of libido. Sulzberger found hormonal therapy to be a valuable adjunct in 33 1/3% of his series of cases. (No further statistics were noted).

Horne, S. F. (43) reported the treatment of 12 white, female patients, with resistant acne, by a combined therapy involving oral estrogens and systemic chorionic gonadotropins. The patients' acne had a duration prior to this treatment of from 2 to 10 years, and were cases which were resistant to conventional forms of therapy, including superficial x-ray therapy. A three month course of treatment was instituted consisting of 0.3 mg. of premarin daily for 20 days, beginning the 5th day of the cycle and 500 IU of APL given i.m. three times a week during the last 2 weeks of the cycle. Horne believed that the value of such a regime could hardly be doubted since improvement was noted in all cases and complete clearing in 50% of his series. Improvement occurred gradually over the 3 month period. There were no undesirable reactions.

Goeckerman, W. H. and Wilhelm, L. F. (44) used estrogens, chiefly ethinyl estradiol, conjugated estrogenic substances and water-insoluble forms, in the treatment of all forms of acne vulgaris in the female. After 10 years of experience with this form of therapy, they are convinced that the estrogens do not merely neutralize excess androgens, but more likely "stimulate every glandular organ in the body". The beginning dose is the smallest acceptable therapeutic dose, which is increased as judgment indicates from the clinical appearance of the patient and the acne. Treatment is continuous if well tolerated. No statistics are noted.

White, Col. C. B. (45) reported on a series of 97 males with acne, who were treated with oral estrogens. All patients were from 17 to 25 years of age; had moderately severe to severe acne, and were observed for a period of at least 3 months. Fourteen hospital patients, serving as a test group and twelve hospital patients serving as a control group were treated with general conservative measures till a base line was established at the end of two weeks. The control group was selected without the knowledge of the doctors observing the patients, and each of the test group received a minimal dose of 40 mg. per day times 20, of diethylstilbestrol to a maximal dose of 154 mg. times 77. The average total dosage was

88mg. times 50. The control group received a placebo. Five unbiased dermatologists observed the patients and noted in each group a slow, but undramatic improvement. An outpatient series of patients consisted of 21 test patients and 50 controls. The clinic patients did no better or worse than the controls. Thus, in the combined series, satisfactory improvement was noted in 20 of the 35 patients, while in the control group, satisfactory improvement was noted in 35 of the 62 patients. The study was inconclusive.

Becker (38) in a series of 58 patients with deep pustular acne, treated with diethylstilbestrol, noted improvement in 53, 3 cured and 2 failures. In the women, diethylstilbestrol was given in doses of 0.25 mg. to 0.5 mg. every day from the 7th day after the completion of one cycle to the onset of the next; and in doses of 0.25 mg. to 1.0 mg. every day continuously for 3 to 4 months in the males. Antibiotics were used in 80% of these cases to control the eruption. This method thus seemed particularly effective when the acne developed after age 20. Becker found estrogens to be of little value in the treatment of chronic, superficial lesions, having a 15% failure in a group of 51 patients.

The method of endocrine therapy of Crowe, F. W. and Curtis, A. C. is outlined in the 1954 Current Therapy (39). This method is similar to other cyclic administration

regimes and involves daily doses of 0.25 to 0.5 mg. per day of diethylstilbestrol or 0.625 mg. of premarin for the first 18 days of each cycle and discontinuing the estrogen with the onset of the succeeding cycle. In males, either of the above drugs are recommended for short periods, i.e. 10 days per month, and side reaction calling for immediate and complete cessation of medication.

XI Summary

The consideration of the endocrine therapy of Acne Vulgaris has been introduced as a subject for a senior thesis. Its importance, sexual and age incidence have been defined. The clinical observations which have suggested a possible endocrinological etiology have been noted. Thus its onset at puberty, exacerbations with pregnancy and menstruation, its occurrence in association with masculinizing tumors, its absence in the eunich and castrate have suggested that a hormonal imbalance is a factor in the development of acne. Laboratory and experimental evidence suggesting this fact has also been presented, including the acneic response of the pilosebaceous apparatus following injection of androgens. The relative increase in the amount of blood and urinary androgens in relation to estrogens has been reported in acneic patients, as has laboratory evidence to the contrary. A number of commonly accepted etiologic factors of acne have been listed, i.e. age, puberty, adolescence, constipation, menstrual disorders, focal infections, seborrhea of the scalp, dietary allergies, fatigue and contact innoculation. The pathology of the disease, acne has been defined and the pathogenesis of the lesions and the pathologic physiology have been outlined. The problems encountered in clinical case studies have been examined and the special problems involved in the

study of therapy of Acne Vulgaris have been recognized. Thus the multiplicity of etiologic factors, its spontaneous remissions, the difficulty of obtaining good controls, and the difficulty in standardizing clinical description of lesions, make the evaluation of therapy of a disease such as Acne Vulgaris a difficult problem..

Since hormonal therapy is by no means universally recognized and certainly must be considered only after less radical methods have been shown to fail, the student has listed general considerations in the conservative management of Acne Vulgaris. Steps have thus been outlined to improve the general hygiene of the skin and scalp, decrease the secretion of the sebaceous glands, to lead to exfolliation of hyperkeratotic areas, combat secondary infections, and evacuate cystic lesions. Indications for hormonal therapy of acne have been reported to be the presence of menstrual exacerbations and the failure of more conservative measures. Comtraindications for endocrine therapy of acne have been listed as (1) patient below 18 years of age, (2) endometritis, (3) chronic cystic mastitis, (4) cervical or endometrial polyps, (5) fibroids, (6) any suspected malignancy of the genital organs or breasts, (7) tendency toward gynecomastia.

The recent literature reporting the use of estrogens by the oral route in the therapy of Acne Vulgaris has been reviewed. Though much of the work reviewed lacks any attempt at a control, and is vague due to the absence of statistics, it appears that most investigators have had reasonable success, either through the use of estrogens alone or in conjunction with chorionic gonadotrophins. Although only the use of estrogens have been reported in this paper, the student reviewed most of the literature concerning hormonal therapy by any route in the preparation of this paper; and it cannot be said that there is any one most advantageous route. This means of therapy at present seems to be a valuable means of treating acne in women whose lesions resist less radical methods of therapy, and to a lesser degree resistant acne in men.

XII Conclusions

Acne Vulgaris is a disease with a complex etiology and complex therapy. Small doses of oral estrogens, given cyclically and perhaps continuously, are an acceptable method of therapy of acne vulgaris in women; particularly those in which there are menstrual exacerbations of the disorder or whose acne has proven resistant to more conservative methods of therapy.

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Bibliography

1. Tobias, N.; Essentials of Dermatology. 4th ed. Philadelphia, Pa., J.B. Lippincott Co.,1952, p.471.

2. Pick, R.; Acne und innere Sekretion. Arch.f. Derm.u Syph. 131:350,1921.

3. Bloch,B.; Metabolism,Endocrin Glands & Skin Disease, with Special Reference to Acne Vulgaris and Xanthoma. Brit.J.Derm.& Syph.43:61,1931.

4. Hollander, L.;The Role of theEndocrine Glands in the Etiol. & Treat. of Acne: Preliminary Report. Arch. Dermat. & Syph.3: 593,1921.

5. Schamberg, J.F.;Research Problems in Dermatology . Arch. Dermat. & Syph. 4: 293,1921.

6. Mumford, R.; Acne Vulgaris, a Symptom not a Disease. Brit. Med. J. L:141,1933.

7. Lawrence, C. H.; The Anterior Pituitary -Like Hormone. A Clinical Study of its effects in Acne Vulgaris. J.A.M.A. 106:983,3/36.

8. Payne,S. A.; Estrogen Therapy in Acne- Contraindications. Annals of West. Med. & Surg. 6:92,2/52.

9. a. Sulzberger, M. B. & Wolf, J.; Dermatologic Therapy in General Practice. Ed. 1, Chicago, Year Book Publish. Inc. , 1940,304.
   b. Sulzberger, M. B., Addenbrooke, E.F., Joyce, S.J. et all; Tropical Acne. U.S.Nav.Med. Bul. 46:178,1946
   c. Ibed; Tropical Acne.Bul.U.S. Army Med Dept. 6:149,1946
   d. Sulzberger, M. B. & Witten, V.H., Hormones and Acne Vulgaris, Med. Clin. of N. Amer. 35:1373.1951.

10. Goldzieher, M. A.; The Endocrine Pathogenesis & Treatment of Acne Vulgaris, Med. Rec. 160:725,1947

11. Hamilton,J.B.; A Prime Factor in Acne. J.Clin Endo.. 1: 570,1941.

12. Geist, S.H.; Salmon, U.J., Gaines, J.A.,and Walter,R.I.; Biologic Effects of Androgens in Women, J.A.M.A. 114:1539,4/1940.

13. Selye, H.; Textbook of Endocrinology, University de Montreal, Montreal, Canada, 1947.

14. Rony, H. R.& Zakon,S.J.; Effect of Endocrine Substance on Adult Human Scalp, Arch. Derm. & Syph. 52: 323,11/45.

15. Butcher, E.U. & Parnell,J.P.; The distribution and Factors Influencing the Amount of Sebum of the Skin of the Forehead. J.Invest. Dermat. 1:31, 1948.

16. Hooker, R. & Pfeiffer, C.A.; Effect of Sex Hormones upon the rat. J. Endo. 32: 69,1943.

17. Barber, H. W.;The Influence of Sex Hormones on the Skin and Pilosebaceous System - Modern Trends In Dermatology, R.M. Mac Kenna, N. York. , Paul B.Hoeber, Inc.,1948, p112.

18. Reiss, F. & Gellis, S.; Effects Produced on the Pilosebaceous System & The Adrenal of the Rabbit by Inunction of Sex Hormones. J. Invest. Dermat. 12: 159,6/49.

19. Mulligan, R. M, & Becker, D. L.; Residual Tissue changes in Male dogs following cessation of orally administered stilbesterol. Amer. J. Path. 23: 299, 1947.

20. Rosenthal, T & Kurzrok, R.; Excretion of Estrin in Acne, Roy. Proc. Soc. Exper. Biol. & Med. 30: 1150, 1933.

21. Wile, U. J., Snow, J.S., & Bradbury, J.T.; Studies of Sex Hormones in Acne, Arch. Derm. &Syph. 39: 195, 1939.

22. Lawrence, C. H. & Werthessen, N.T.; The Endocrine Dyscrasia of Acne Vulgaris in Women. Endo. 27: 755, 1940.

23. First, A.; Functional Menstrual Disorders: Investigation & Endocrine Therapy -- Symposium of Rec. Advances in Gyn. and Obstetrics, M. Clin. N. Amer. 29: 375(11/45).

24. Gallagher, T.F., etaall; The Daily Urinary Excretion of Estrogenic and Androgenic Substances by Normal Men and Women, J. Clin. Invest. 16: 695, 1937.

25. Rosenthal, T. & Neustaedter, T.; Estrogenic Substance in Blood of Patients with Acne, Arch. Dermat. & Syph. 32: 560, 1935.

26. Cornbleet,T.& Barnes, B. ; The Hormones and Acne Vulgaris. Arch. Dermat. & Syph. 40: 249,9/39.

27. White, C.B., Peterson, A., et all; Acne Vulgaris and the Urinary 17 Keto-steroids in Young Men, 2:12, 131,12/51.

28. Nathanson, J.T. & Towne, L.W.; Sex Hormones in Urine and Acne, Endo: 28: 851, 1941.

29. Way,S.C., Andrews, G. C.; Hormones and Acne, Arch. Derm. &Syph. 61:575, 4/50.

30. McCarthy, L. & Hunter, O.B.; Failure of Therapy With Glandular Preparations in Acne Vulgaris, Arch. Derm. & Syph. 35: 211, 2/1937.

31. Stokes,J. H. & Sternberg, T. H.; A Factor Analysis of the Acne Complex With Therapeutic Comment, Arch. Dermat. & Syph. 40: 345, 1939.

32. Baird, K.A.; Preliminary & Shor Reports- An Effective Approach In the Treatment of Acne. J. Invest, Dermat. 12: 317,6/49.

33. Andrews, G.C., Domonkos, A.N.,& Post, C.F., Treatment of Acne Vulgaris. J.A.M.A. 146:1107, 7/1951.

34. Kalz,F.; Prichard, H.; Fournier, C., Janauskas,A.; Management of Acne Vulgaris in Private Practice, Canadian Med. Assoc. J. 67: 409, 11/1952.

35. Nyvall, H. Ol ; Treatmentof Adolescent Acne With Endocrines. Urol. & Cut. Rev. 47:685, 12/43.

36. Novy, F. G.; Tropical Acne. Calif. Med 65: 1,1946

37. Fox, E. C. Tropical Anhidrotic Asthenia. Arch. Derm. & Syph. 60: 173, 1949.

38. Becker, F. T.; The Acne Problem, Arch. Derm. & Syph. 67: 173, 1953

39. Ayres, S.; Acne Vulgaris in CurrentTherapy,Conn, Saunders, 1954, 571.

40. Grollman, A. Essentials of Endocrinology, Ed. 2, Philadelphia, J. B. Lippincott, Co. , 1947, 577.

41. Kimbrough, R. A. & Israel, S. L. ; The Use and Abuse of Estrogen, J. A. M. A. 138: 1217, 12/48.

42. Goeckerman, W. H., Hormonal Therapy of Acne Vulgaris In TheFemale, Arch. Dermat. & Syph. 61: 237,2/50.

43. Horne, S. F. The Treatment ofAcne Vulgaris With Estrogens and Chorionic Gonadotropins. Mich. U. Med. Bul. 17:317, 9/51.

44. Goeckerman, W. H. & Wilhelm, F. X., Estrogens in Treatment of Acne Vulgaris, Arch. Dermat. & Syph. 66: 402, 1952.

45. White, Col. C. B.; Lehmann, C. F.; Diethylstilbestrol Therapy In young Men With Acne, Arch. Dermat. & Syph. 65: 601, 1952.