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Stimulation of Hair Growth by Topical Application of Androgens

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Our previous study of senile skin showed the capacity of topical, but not systemic, testosterone propionate to stimulate hair growth in the axilla and on the forearm. As an extension of this finding, androgen creams were applied to the scalps of 21 bald men. Approximately 75% of the group showed some stimulation of hair growth, as indicated by longer, thicker, more pigmented hairs in the bald area. Within five months of treatment approximately 10% to 15% of the follicles were stimulated to produce terminal type hairs. The probability of regrowth is dependent neither on the duration of the baldness nor on the age of the subject. The enhanced growth is not thought to be an expression of the hormonal activity of testosterone, which in predisposed subjects is a prerequisite for common baldness, but rather a pharmacological local effect on the synthetic activities of the underlying connective tissue. These results indicate the possibility of effective prophylaxis against common baldness; however, indiscriminate use of topical testosterone for its treatment, at this stage, is unjustifiable.

Common baldness is a common problem. While not life-threatening, it is of sufficient cosmetic concern and provokes enough anxiety to have promoted a long list of procedures and nostrums. From the earliest prescription in the Ebers Papyrus, a mixture of equal parts of crocodile, lion, hippopotamus, and serpent fat, to the most recent techniques of diathermy and ultrasound, the repeated pattern has been one of promise and inevitable disappointment. Despite manifold claims from legitimate and not so legitimate sources, no verified instance of hair regrowth of any type has ever been authenticated in common baldness. In view of the futility of past experience we submit, with trepidation, an indisputable demonstration of at least partial regrowth of hair.

Gross and Microscopic Evolution

Lest there be any confusion, the commonly used synonyms for this condition are male-patterned baldness, senile alopecia, and idiopathic premature baldness. It is the localization of the disease within circumscribed areas of the scalp which differentiates it from all other forms of alopecia and is responsible for the "patterned" appelation. Clinically, the disease evolves in a characteristic way. It usually begins with an "M"-shaped recession of the frontotemporal area and eventually involves an oval of hair loss in the crown area. These early sites of alopecia progress toward each other, merging and obliterating the remaining bridge of hair, to form a denuded horseshoe-shaped area rimmed by the tonsural and occipitoparietal hair, the "Hippocratic wreath." Once initiated, the process grinds on relentlessly and unremittingly. Spontaneous regrowth is unknown. The condition is never inflammatory, is unaccompanied by scarring, and has no causal relationship to either dandruff or seborrhea. There are never isolated patches of complete baldness as in alopecia areata, and the hair loss is localized solely to the scalp. The patient's typical complaint is not a sudden crisis of diffuse, unusual shedding of resting hair, as may be seen in the postpartum period or following fever, severe illness, or drugs.[1]

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Rather, there is an awareness of gradual thinning and regression, in short, a defect in hair synthesis. Although in final form the scalp is smooth and shiny, close inspection, preferably with oblique lighting and magnification, always reveals the presence of a very fine fuzz.

Dermatologists the world over have become increasingly aware that common baldness, previously regarded as a sex-limited condition of men, affects women in a similar but more restricted pattern. Best known as diffuse hair loss in women, the condition is both grossly and microscopically identical to that in men, except it is more diminutive and rarely reaches an advanced state of complete depilation.[2,3]

Maguire and Kligman, of our laboratories, have studied serial sections from more than 200 cases of

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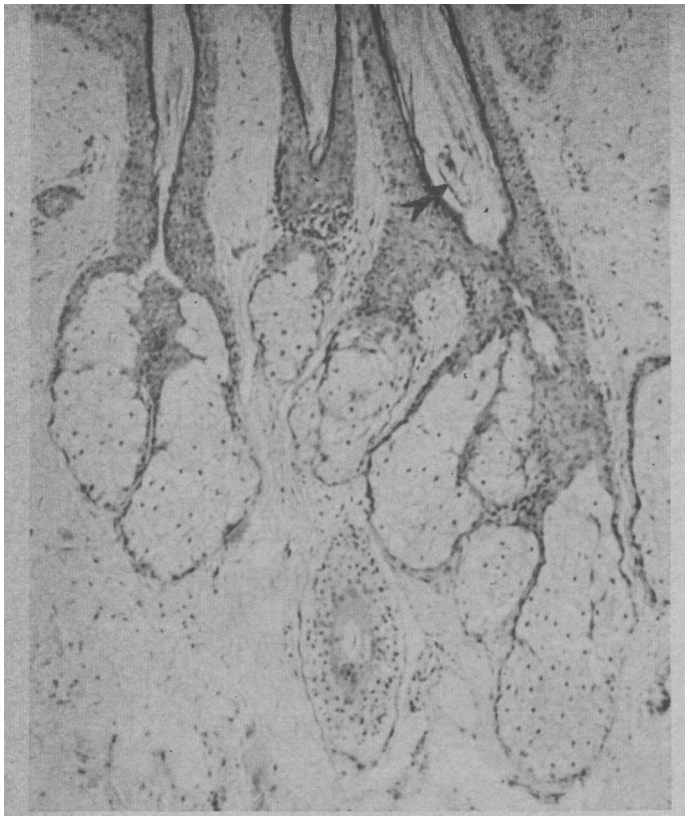

1. Three shrunken follicles from 75-year-old white man with complete baldness. Each has disproportionately large sebaceous gland. One at right contains tiny hair (*arrow*) and has functioning, though rudimentary, pilary apparatus. Two follicles at left still further involuted, have irreversibly lost hair-bearing portions, and cannot respond to testosterone.

common baldness in men and women. They depict the structural changes as follows.[4] Briefly, the characteristic change is a progressive shrinkage of the follicle which produces an ever diminishing hair. Normally scalp hairs are distributed in clusters of three to five follicles, which may have a common opening. Involution does not take place synchronously in members of the cluster. Typically, one or two hairs in the group may have regressed completely, while others remain partly or entirely normal. Follicles are affected completely at random. In the intermediate stages of regression, the shrinking follicle leaves behind a fibrous streamer which originally enveloped the hair as a connective tissue sheath.

During involution, the growing phase, which normally lasts from three to six years, is progressively shortened, inevitably resulting in shorter hairs. In consequence, the proportion of resting "club hairs" increases, finally attaining a majority, in contrast to the normal scalp which contains 90% of growing, anagen hairs.[5] Eventually the hair produced by the receding follicle is a fragile, vellous-like, downy filament, not unlike that of the lanugo of the newborn. Whereas originally the sebaceous gland was a minor appendage of the hair-bearing follicle, these relationships are finally reversed. The hair-bearing portion may become so rudimentary, producing a trivial hair or keratinous dust, that its very presence may be difficult to detect except in serial sections (Fig 1). The pilary portion may ultimately disappear leaving a follicle ending in a sebaceous gland.

The final expression is a complete extinction of some pilosebaceous members of the cluster, leaving no histological trace. These regressive events take place much more rapidly in some individuals than in others. Nonetheless, even at the stage of complete clinical baldness there are always some follicles, no matter how atretic, which produce a minute and inconsequential hair. Unlike the scarring alopecias, some orifices of remaining follicles can still be seen by surface examination. At equivalent stages of clinical baldness the major proportion of follicles have been completely abolished in some individuals, while in others, trivial, but competent, remnants persist. Since it is the consensus that new formation of terminal follicles does not occur in adult life, the possibility of partial restoration is dependent upon the perseverance of a certain number of these competent follicles.

Pathogenesis

Three factors are absolute prerequisites for the development of common alopecia: (1) age, (2) ancestry, and (3) adequate androgens. These variants are interdependent; the absence of any one will prevent baldness.

Age.—The disease never appears before adolescence, but thereafter, for each decade there is an increasing incidence of clinical baldness.[6] Even in unaffected individuals, the aging process itself results in a gradual thinning with histological events entirely comparable to patterned baldness.

Ancestry.—Certain races are more predisposed to baldness. The disease has less severe expression among Orientals and American Indians.[7] Study of family pedigree indicates that the condition is inherited as an incomplete dominant trait.[8] In women, in particular, the high incidence of alopecia in the female forebears emphasizes the genetic predisposition, which may be otherwise obscured by the relative frequency of the condition in men. Advanced denudation in early adult life is generally regarded as a manifestation of the homozygous condition.

Androgens.—Baldness does not appear in those individuals who do not reach sexual maturity, whether through gonadal insufficiency or castration.[9] Castration after puberty in those who are becoming bald arrests the process.[10] Without doubt, the most striking demonstration of the crucial role of androgens, shown in Hamilton's study,[9] is that baldness could be produced in castrates by the administration of testosterone propionate, provided there was a suitable genetic background. Moreover, masculinizing syndromes in women may precipitate rapidly advancing patterned baldness.[11] The onset and development of baldness in normal individuals is, however, not related to differences in endogenous testosterone production. It is the target sensitivity of individual follicles which determines the response. It should be emphasized that the maturation and maintenance of scalp hair is not dependent

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on androgens like that of the beard, axilla, and pubis, which are secondary sex characteristics. Male hormones only figure in the loss, not the support of scalp hair. There is no parallel between waning sexual function in age and any reversal of the trend of alopecia, as there is a correlation between loss of secondary sex hair and diminishing steroid production.[7] It is one of the mysteries of biology that the same hormone, testosterone, simultaneously produces hair growth of the beard and hair loss of the scalp in castrates.

Materials and Method

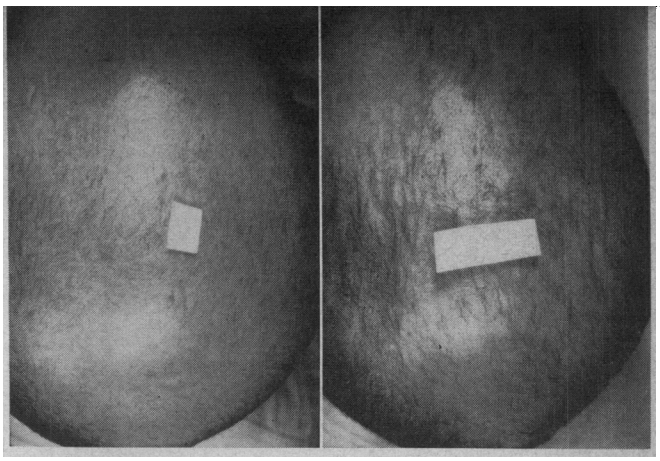
Forty-one institutionalized men with complete frontocentral denudation served as subjects for this study. The men were either inmates of the Philadelphia County Prison or residents of the Riverview Home for the Aged. All had periodic, complete physical examinations and were free from any obvious infirmity, or renal, hepatic, or prostatic disease. The age distribution (29-78 years) and duration of baldness (1-30 years) were quite varied (Table). Each of 21 subjects in the test group had approximately 0.5 gm of 1% testosterone propionate in hydrophilic ointment applied once daily to the scalp by trained personnel. The remaining 20 men in the control group were similarly treated with the vehicle alone. The duration of the original study in 16 of the subjects in the androgen-treated group was five months. Subsequently it was learned that this was insufficient time to bring about maximal effects, and in five subjects applications were continued for periods up to one year.

In this preliminary study, no effort was made to quantitate the amount of regrowth of hair. A positive response to testosterone propionate ointment was the unmistakable appearance of longer, stouter, terminal type hairs in an area which previously contained nothing but nearly invisible lanugo-type hairs. By this criterion 16 of the 21 androgen-treated subjects showed indisputable hair growth. None of the control group treated with hydrophilic ointment showed this change. We judged that perhaps 10% to 15% of the original follicular population was stimulated (Fig 2). The pattern of regrowth progressed in the reversed order of loss; greater response was noted about the parietal and occipital area. These peripheral areas, adjacent to surviving terminal hairs, reacted earliest and best. Evidently the most recently and incompletely involuted follicles are capable of optimal response.

Topical Application of 1% Testosterone Propionate in Hydrophilic Ointment

Subject No.	Age, Yr	Race	Approximate Duration of Complete Baldness, Yr	Result
1	78	W*	30	+†
2	75	W	30	0†
3	72	W	30	0
4	43	N*	10	+
5	50	N	11	+
6	45	N	12	+
7	50	N	25	+
8	43	W	12	+
9	59	W	12	0
10	43	N	4	0
11	38	N	5	+
12	36	N	1	+
13	51	N	10	+
14	46	N	15	0
15	45	W	14	+
16	53	N	13	+
17	37	W	8	+
18	47	N	11	0
19	52	N	5	+
20	29	W	7	+
21	32	W	5	+

* W = White; N = Negro.
† 0= no visible change in bald area; + = development of terminal hairs.



2. *Left*, Scalp of 38-year-old Negro male bald for five years. *Right*, Same scalp after five months of testosterone propionate ointment application. Longer and thicker terminal hairs have appeared in scattered fashion.

The age of the subject, whether young or old, did not appear to affect the probability of stimulation. Surprisingly, we have the tentative impression that the result was not clearly dependent on the duration of baldness (Fig 3). A return of pigmentation in white-haired individuals was not observed. Although the regrowing hairs were terminal and coarser, they probably did not reach the length and thickness of which the follicle was originally capable. In no instance was there a restoration of a thick, luxuriant pelage which wiped out the impression of baldness.

Within the short period of this study no individual was adversely affected by the treatment. There was no evidence of salt retention, prostatic hypertrophy, or return of axillary or pubic hair in older individuals. Although difficult to document, the three most elderly subjects experienced improvement on mood, vigor, and appetite, which impressed the attending personnel as well as the subjects, perhaps reflecting the anabolic activity of testosterone.

Comment

The informed physician presented with a therapeutic suggestion to treat common baldness topically with testosterone propionate ointment would not only be obliged to reject the proposition as contrary to biological knowledge, but would doubtlessly question the sanity of the presenter. It, therefore, behooves us to explain the events which led to this improbable experimental activity.

In a prior study of the effects of topical steroids on aging skin, we were able to demonstrate that

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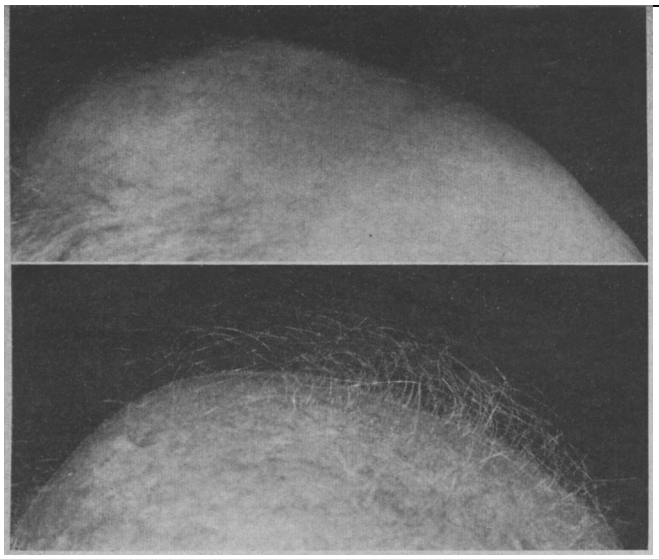

3. Scalp of 78-year-old white man bald for 30 years. *Top,* Clinically scalp appears completely bald, except at sides, but close inspection shows barely perceptible fuzz of tiny, downy hairs. *Bottom,* Same scalp after nine months of topical testosterone. Fine lanugo-type hairs have become coarser and longer. Only follicles which had not completely involuted responded to testosterone, probably no more than 10% of follicles.

testosterone propionate produced both increased hair growth and exocrine sweating in the axillae of aged individuals. This effect was purely local and not obtainable by systemic administration of the hormone. From this it was judged that the response was not a physiological reactivation of a hormone-dependent tissue.

Microscopic examination furnished some clues with regard to the mechanism of this change. It was noted that the thin, inactive fibroblasts became larger and more numerous with increased secretory activity, as revealed by a greater amount of acid mucopolysaccharide ground substance.[12] These dermal changes which centered on the connective tissue "master cell" were reflected by cytological improvement in the senescent atrophic epidermis. Similar microscopic changes have been observed in the axilla, face, and forearm. There is ample experimental evidence that the cutaneous epithelial structures require support on a physiologically-adequate dermis for continued function and differentiation.[13] It is worth emphasizing that the changes effected by testosterone propionate are obtainable only by high topical concentrations of the androgen and not by oral or parenteral administration. We have conjectured that the effects obtained by topical treatment are direct, as if one were dealing with an organ culture isolated from the rest of the body. Testosterone stimulates fibroblasts in tissue culture.[14] On the other hand, it is the circulating androgens which control the course of patterned baldness, an effect which is almost certainly indirect and as yet unexplained. It was our awareness that this androgen was operating locally to produce similar histological and histochemical responses in various senescent areas, in both sexes of varied ages, that led us to apply it to the bald scalp. We envisioned that the direct action of testosterone, probably reflecting a pharmacological rather than a hormonal effect, would overcome the opposing tendency of the circulating androgens to incite hair loss.

Although Maguire, by the repeated injection of large amounts of testosterone cypionate in the beard area of elderly women, succeeded in producing terminal hair, we were unable to stimulate growth in the bald scalp by the same method.[15]

It would not appear difficult to explain why there was not a complete regrowth of scalp hairs approaching the original density. Anatomical study shows clearly that at the stage of complete baldness, even in recently developed cases, there is an annihilation of many follicles of the clusters, while others scarcely survive as rudimentary hair-bearing units. Since we peremptorily reject the idea of neogenesis, the possibility of hair stimulation is absolutely dependent on the survival of competent follicles which have not reached the stage of complete or near complete degeneration. We call attention to the fact that though all truly bald subjects are clinically alike, they differ considerably in the degree to which the follicles are preserved. For example, we have obtained our best result in a 78-year-old man, who on anatomical study of thick whole mounts had many more surviving follicles than other subjects.

With this research experience, it is possible to reexamine the skeptical outlook of many physicians that common baldness is a totally irreversible process. This pessimism stemmed from the long list of ambitious, unfulfilled, therapeutic claims. The rampant commercialism of various trichological enterprises which prey upon the hopeful has further strengthened this disbelief. Nonetheless, evidence of reversibility was already at hand. Women with patterned baldness accompanying masculinizing syndromes have indeed experienced considerable regrowth after elimination of the androgen-secreting lesion.[11] This largely incidental observation of endocrinologists might have opened the mind to the research possibilities.

It is almost impossible to exaggerate the significance that scalp hair has for the human psyche. Historically it has been woman's crown of beauty and man's symbol of strength and vigor. The impact of its painful loss, by whatever means, has furnished dramatic material from biblical to modern times, eg, the story of Sampson and Delilah and the shaving of French women who "collaborated" with their wartime enemies. We know only too well that bald people grasp at hairs and cherish every fiber. They are ready to be gulled, deceived, and deluded. We are fearful of the misinterpretation and misapplication of this work in the face of such intense feeling. We would strongly counsel against the indiscriminate use of testosterone. This is a potent hormone and its long-term use in an unsupervised population is to be condemned. Its use is obviously ruled out in females of the reproductive age. Testosterone happens to be one of the few substances which is rather well absorbed through the skin. For instance, its rate of penetra-

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tion exceeds by manyfold the rate of corticosteroids.[16] Under optimal circumstances, with occlusion, we have demonstrated more than 50% absorption in 24 hours. This could mean as much as 1 mg/day entering the system or approximately one quarter the normal endogenous production of young men.[17] Although we have encountered no adverse effects one must bear in mind the action of testosterone which might be harmful, namely, salt retention in individuals with cardiac disease, stimulation of hyperplasias and neoplasms of the prostate, and, with long-term administration, even atrophy of the testes, probably due to inhibition of pituitary gonadotropins. These limitations are less applicable in postclimacteric, healthy individuals who may, in fact, experience some anabolic benefits.

We do not regard that we have achieved a useful treatment for common baldness by topical administration of testosterone. The real significance of this research lies in its opening of a door for investigating the creation or discovery of other compounds which might have almost purely local effects. In this connection one may cite the lesser, but definite ameliorative, effect of pregnenolone, a precursor of testosterone, on senescent skin.[18] Moreover, the beneficial effect of progesterone on aging skin has been interpreted by us to stem from its conversion to an androgen-like substance. Worthy of immediate attention are certain steroids on the metabolic pathway of testosterone, eg, dehydroepiandrosterone, which are in themselves weak androgens. We are presently examining the effects of these substances in balding males and females. While our studies of topical application of testosterone in postclimacteric females with common baldness are incomplete, we anticipate identical results.

At present this work is of interest mainly because of its biological implications. If topical applications are to acquire genuine usefulness in common baldness, the major emphasis must be in prophylaxis. There is every reason to believe that treatment in the early stages will be far more effective in arresting the process than the limited regrowth we have obtained in the late stage of denudation. We cite here the only case of recent partial baldness that we have treated with this method. The subject, with a patch of baldness on the crown, has responded quite impressively after only three months of topical application of testosterone propionate. The procedure of applying 1% testosterone propionate in hydrophilic ointment once daily is strictly empirical. We are currently studying other concentrations and administration schedules to determine the optimum conditions of use.

This study was aided by Mr. R.S. Groller, director, and residents of the Riverview Home for the Aged, Philadelphia, and Mr. E.J. Hendrick, director, and inmates of the Philadelphia County Prison.

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CORRECTION

Where Credit Is Due.—In the original contribution titled "Acute Pharyngitis and Tonsillitis in University of Wisconsin Students" (**190**:699-708 [Nov 23] 1964), an error occurs on p 705, in the first paragraph under "Clinical Diagnosis." The sentence beginning, "In children, certain combinations of features such as intense pharyngeal edema. . . ." actually represents work done by M. Stillerman and S. H. Bernstein and was reported in an article titled "Streptococcal Pharyngitis: Evaluation of Clinical Syndromes in Diagnosis" (*Amer J Dis Child* **101**: 476-489 [April] 1961).

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