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Relationship of urinary 17-Ketosteroids to Idiopathic premature baldness

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"THE RELATIONSHIP OF URINARY 17-KETOSTEROIDS TO IDIOPATHIC PREMATURE BALDNESS"

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I. INTRODUCTION

Idiopathic Premature Baldness has been a cosmetic malady endured throughout the ages by man. It has been estimated by Snyder[23] that 43% of the male population will become bald. Idiopathic Premature Baldness has its onset at about 16 years of age and nearly reaches completion at 30 years of age.

Aristotle noted premature baldness, in his day, and quite surprisingly, correlated his observations with increased sexual activity. Many myths and unfounded correlations followed Aristotle's postulation. In 1898 Darwin noted in his study, "The Expression of the Emotions in Man and Animal",[5] the muscles of Man's scalp are now useless vestiges of muscles once used to retract the ears and tighten the scalp in preparation for combat. Johnson[10] correlated the chronic activity of the scalp muscle vestiges and baldness. Many other reasons for baldness were set forth by psychiatrists and dermatologists, until Osborn[16] in 1916 postulated evidence toward a genetical relationship. Finally, in 1942 Hamilton[7] noted a hormonal correlation to premature baldness, in his work with eunuchs.

It has been found testosterone will initiate premature baldness in eunuchs herediterically predisposed, however, no correlations have been made to determine whether or

not higher testosterone production is found in those individuals with Idiopathic Premature Baldness as opposed to those without this malady.

It is the purpose of this paper to correlate the 17-Ketosteroid urinary excretion, used as an index of androgen production, in the non-bald and Idiopathically Premature Bald Individuals.

II. Review of Conditions Contributing to Idiopathic Premature Baldness

(a) Seborrhea Oleosa

This skin affliction has been known for many years as a common disease of the scalp and body. Seborrhea Oleosa presents with an increased sebaceous gland activity, scaling, itching, and hair loss. Sabouraud mentioned this disease as a probable cause of baldness, however, Agnes Savill's[20] book presented this view quite clearly. She states: "In a case of severe Seborrhea Oleosa the usual course is at first rapid then a gradual march toward complete baldness with a stretched glossy skin, which is so frequently seen in men." Vickers[25] substantiates and supports these views. These views are well taken. It is, also, interesting to note a strong relationship to sebaceous gland activity by the androgens has been observed by several individuals. One unexplained facet, however, is the fact other hairy areas of the body are affected by seborrhea without permanent loss of hair.

(b) Tightly Fitting Hats

Benjamin Dorsey[6] postulated baldness may be caused by tightly fitting hats and coined the term for this type of baldness as "Traumatic Baldness". He believed the pressure of the

hat band created chronic ischemia and premanent blood vessel damage, which led to tissue destruction and consequent hair loss. These hypothesis are interesting but do not explain baldness in individuals who do not wear hats.

(c) Tension

Young[26] presents this theory in that scalp tension leads to reduction in the thickness of soft tissues and interference of circulation, with consequent hair loss. Szasz[24] supports these views and adds the shearing action of muscles to contribute in the damage of the hair follicles through ischemia.

These points are well taken, however, they do not explain the fact the same forces seen in man are in effect in women but, strangely, do not lead to female baldness.

(d) Heredity

Rattner[18], Osborn[16], Harris[9], and others have demonstrated a definite correlation between genetics and premature baldness, which, undenyingly, must play a significant role in the etiology of premature baldness.

(e) Hormones

Hamilton[7] found:

1. Baldness does not develop before puberty or adolesence.
2. Adult eunuchs who were castrated prior to adolesence do not become bald.
3. Twelve individuals were beginning to become bald prior to castration. The march of baldness ceased following castration.
4. Twelve prepubital castrates were treated with testosterone and four began to become bald. The remaining eight did not become bald. The four individuals demonstrating baldness had a family history of premature baldness while the other eight did not.
5. Baldness frequently occurs secondarily to masculinizing tumors, such as arrhenoblastomas in women.

Hamilton supports strongly, the hormonal viewpoint and does not disallow the hereditary aspects of Idiopathic Premature Baldness.

III. PATHOGENESIS OF PREMATURE BALDNESS

Whether the cause of Idiopathic Premature Baldness be hormonal, herediteric, physical, or a combination of these causes, once the pathological march of baldness begins it seems to be an irrepairable process. Kligman[13] describes this march as the normal life cycle of the hair follicle being halted and the hair passing through histological phases i.e. (telegon and anagon) until alopecia is reached.

Cormia[4] noted the blood supply of the scalp decreases progressively with increasing age. He found the amount of reduction seems to be directly proportional to the diminution in the metabolic needs of the follicle. Here again one may postulate that a diminution in the metabolic needs of the follicle must be influenced by some body hormonal secretion, such as perhaps, estrogen in the female and testosterone in the male. Cormia, also, noted the scalp skin increasing in thickness with age, and that bald people usually had slightly thicker skin over the scalp than did the non-bald. One could postulate the thickened skin as being a secondary manifestation of decreased blood flow.

IV. THE MECHANISM & RELATIONSHIP OF URINARY 17 KETOSTEROIDS TO PREMATURE BALDNESS

Human urines contain steroids carrying ketogenic oxygen at C17, some of which, are phenolic while others are neutral. The latter are commonly called 17 Keto-steroids. The principal members of this group are:

(1) Androsterone

(2) Etiocholanolone

(3) Isoandrosterone

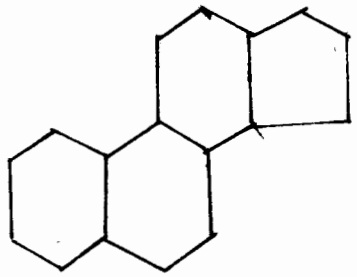
(4) Dehydroisoandrosterone

(5) Androstanedione

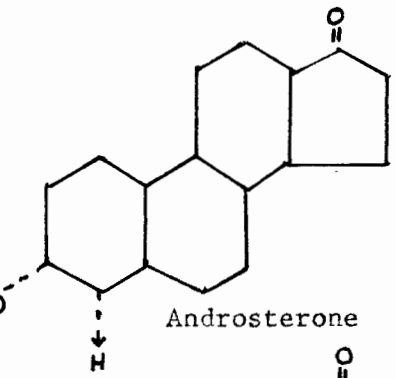
(6) Androstenedione

The chemical structures are presented in Figure 1. One third of the Androsterone and Etiocholanolone arise in the testes while the remaining two thirds is produced in the zona reticularis of the adrenal cortex. Androsterone and Etiocholanolone are found in larger amounts than any other urinary 17 ketosteroids. Etiocholanolone does not, however, possess androgenic activity as does androsterone. Zimmerman.[28]

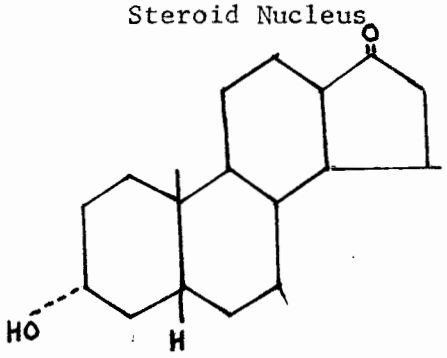
The basic chemical structure of the 17 ketosteroids is the perhydrocyclopentanophenanthrene ring. The 17 ketosteroids,



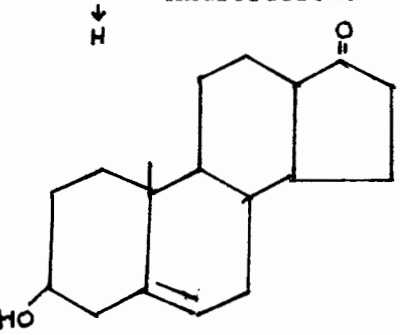
Steroid Nucleus



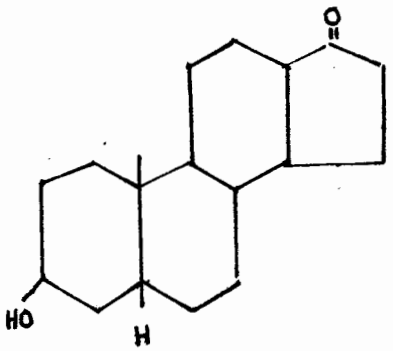
Androsterone



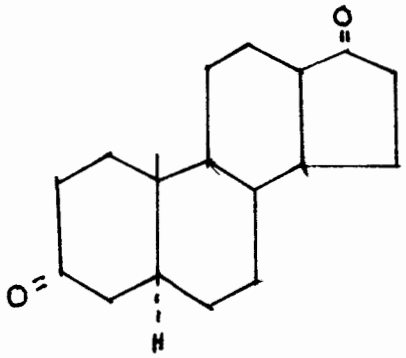
Etiocholanoione



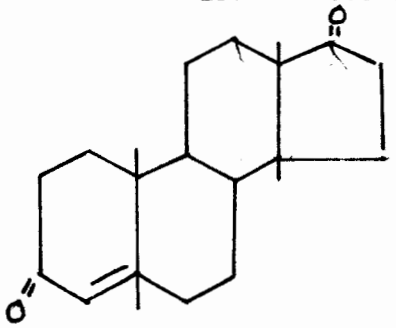
Dehydroisoandrosterone



Isoandrosterone



Androstanedione



Androstenedione

Figure 1.

for the most part, can be looked upon as derivatives of two hydrocarbons: androstone and Etiocholone, which are distinquished from each other by the steric configuration around the fifth carbon atom. Zakarycheva.[30] The 17 keto-steroids have a keto group at carbon atom number 17. This property makes their colorimetric determination possible by means of the Zimmerman Color Reaction.[29]

Testosterone produced in the testes proceeds through the V. Spermatica in its normal state. Ultimately, this testosterone is metabolized, mainly, in the liver and to a lesser degree in the kidney by unknown enzymes to its metabolites of androsterone and etiocholanolone, which are then excreted in the urine. Axelrod.[2] See Fig. 2.

Callow and Callow[3] provided one of the first good chemical assay methods of 17 ketosteroids, which was a modification of the Zimmerman Reaction.

Hamilton[7] noted an increase in sebaceous secretions and loss of hair with testosterone therapy in eunuchs, predisposed to baldness through heredity.

Therefore, on the basis of the above discussion the analysis of urinary 17 ketosteroids is a logical and reliable

manner in which to measure, indirectly, androgen production in the body.

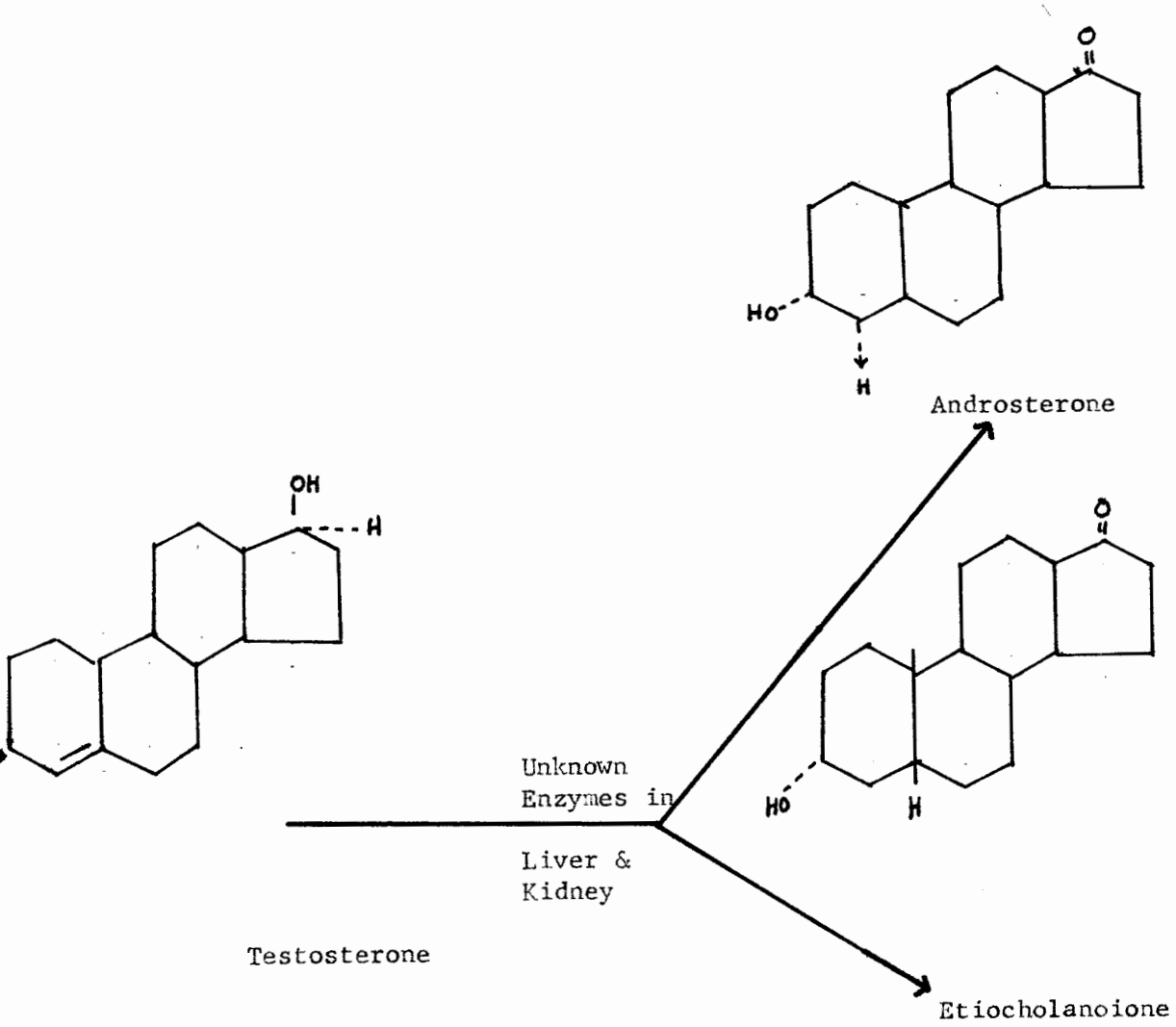

Androsterone
Unknown
Enzymes in
Liver &
Kidney
Testosterone
Etiocholanoione

Figure 2.

V. LABORATORY APPROACHES TO THE DETERMINATION OF THE URINARY EXCRETION OF 17 KETOSTEROIDS IN PREMATURE BALDNESS

(a) Materials

Fifteen individuals in good health, who did not demonstrate evidence of premature baldness, and whose age group fell in the twenties and early thirties were chosen as the control group. Fifteen individuals in good health, who did demonstrate evidence of premature baldness, in the same age grouping as above, were chosen as the test group.

Twentyfour hour urine collections were made on all individuals, in containers with a toluene derivative, (1.5 cc.), as a preservative.

(b) Methods

1. The urine samples were allowed to sit for 1 hour for all the toluene derivative to layer the surface.

2. A measured aliquot was withdrawn beneath the layered toluene, and frozen until the time of analysis.

3. Total urinary volumes were calculated and recorded.

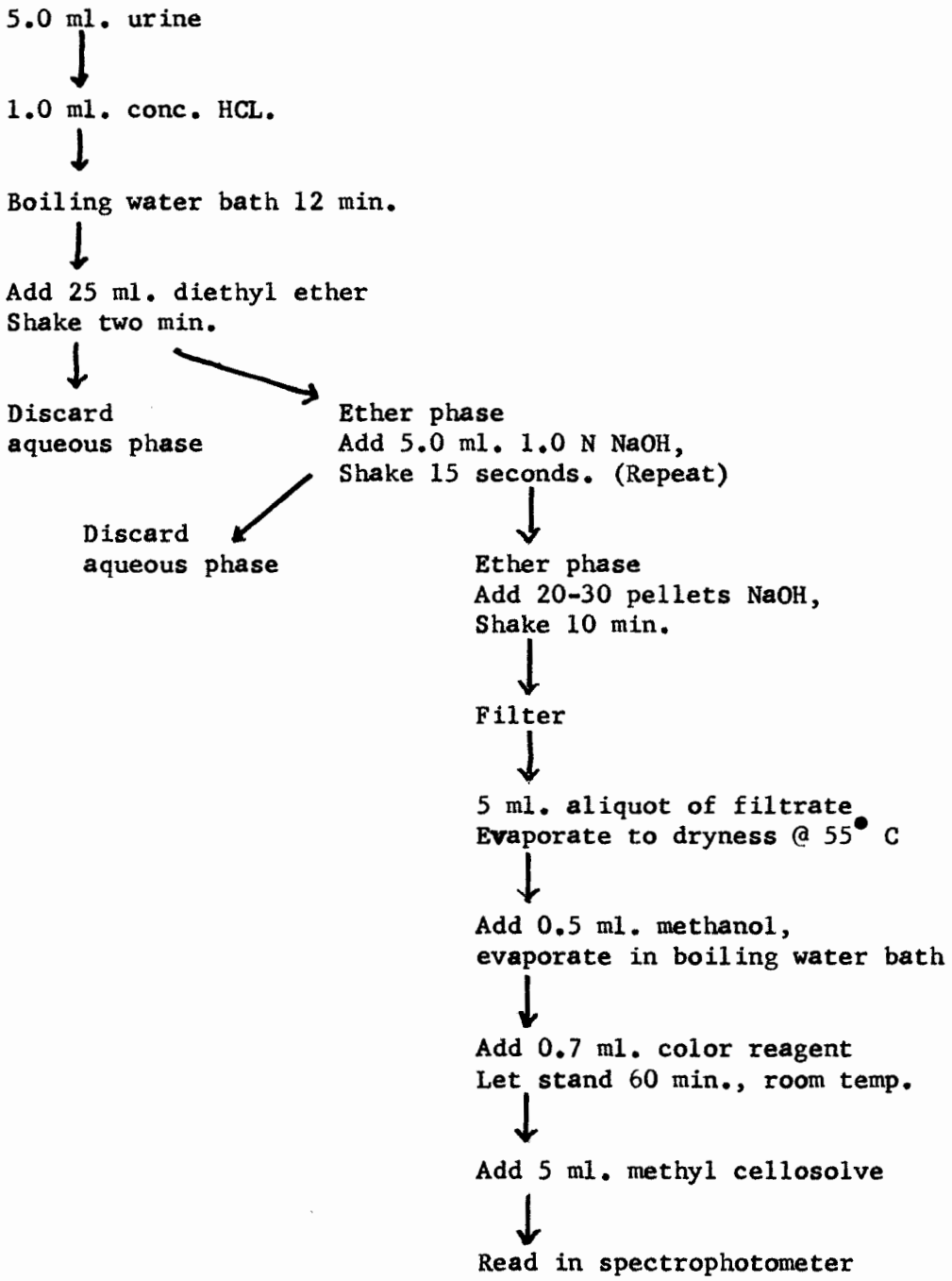
4. The specimens were analyzed utilizing the Modified Zimmerman Reaction. Zenker.[27] In this reaction the 17-Keto group is coupled with m-dinitrobenzene to form colored complexes in the green spectrum. The intensity of color can be measured at 520 mu with the Photoelectric Colorimeter. A standard curve is prepared using known amounts of pure crystaline 17-Ketosteroid, and the unknowns plotted on the curve to determine their value. Hawk.[29] A simplified schematic flow sheet is seen in figure 3 representing the analytical method.

5. Actual Values are calculated by plotting the % transmittance of the standard on semilogarithmic paper and the concentrations of the specimens (C_x) noted. Then the Mg. / Specimen = 1 C_x x Specimen Volume (liters). Normal Values (mg./24 hours) are noted below.

Age (years)	Less/2	2-5	5-10	10-15	15-60	60-90
Males	0.5-1.5	-3	3-6	6-15	10-20	20-50

These values are somewhat above those reported by Paschkis.[17]

FLOW CHART OF 17-KETOSTEROIDS METHOD
(Modified from Zenker and Biskind)[27]



(c)

CONTROL GROUP

Sample No.	Urine Volume	Mgms. 17-Ketosteroid/24 hrs.
#1	1525 cc.	13.25
#2	1100 cc.	10.45
#3	1550 cc.	13.96
#4	1420 cc.	14.76
#5	1300 cc.	15.20
#6	1200 cc.	11.76
#7	1100 cc.	9.90
#8	1530 cc.	9.40
#9	2000 cc.	12.60
#10	1160 cc.	8.60
#11	1200 cc.	9.60
#12	1645 cc.	8.90
#13	1650 cc.	13.05
#14	1050 cc.	10.50
#15	1800 cc.	14.43

Mean Mgms. Ketosteroid/24 hours of the Control Group = 11.764 mgms.

TEST GROUP

Sample No.	Urine Volume	Mgms. 17-Ketosteroid/24 hours
#1	800 cc.	9.42
#2	925 cc.	12.23
#3	1280 cc.	25.98
#4	940 cc.	11.46
#5	1250 cc.	11.87
#6	1500 cc.	8.70
#7	1100 cc.	14.85
#8	1770 cc.	9.74
#9	1010 cc.	12.02
#10	1540 cc.	9.25
#11	905 cc.	13.85
#12	955 cc.	11.75
#13	950 cc.	9.60
#14	1400 cc.	9.10
#15	1500 cc.	20.00

Mean Mgms. Ketosteroid/24 hours of the Test Group = 12.655 mgms.

VI. STATISTICAL ANALYSIS OF DATA

Statistical analysis of data will be carried out using the "t" test due to the number of specimens to be analyzed.

CONTROL GROUP

	x	$x - \bar{x}$	$(x - \bar{x})^2$	x^2
#1	13.35	+1.586	2.515	178.223
#2	10.45	-1.314	1.727	109.203
#3	13.96	+2.196	4.822	194.832
#4	14.76	+2.996	8.976	217.858
#5	15.20	-3.436	11.806	231.040
#6	11.76	-0.004	0.000	138.298
#7	9.90	-1.864	3.475	98.010
#8	9.40	-2.364	5.589	88.360
#9	12.60	+0.836	0.699	158.760
#10	8.60	-3.164	10.011	73.960
#11	9.60	-2.164	4.683	92.160
#12	8.90	-2.864	8.203	79.210
#13	13.05	+1.286	1.654	170.303
#14	10.50	-1.264	1.598	110.250
#15	14.43	+2.666	7.108	208.225
Total	176.460	0.000	72.866	2148.742

TEST GROUP

	x	$x - \bar{x}$	$(x - \bar{x})^2$	x^2
#1	9.42	-3.235	10.465	88.736
#2	12.23	-0.425	0.181	149.573
#3	25.98	+13.325	177.556	674.960
#4	11.46	-1.195	1.428	131.332
#5	11.87	-0.785	0.616	140.897
#6	8.70	-3.955	15.642	75.690
#7	14.85	+2.195	4.818	220.523
#8	9.74	-2.915	8.497	94.868
#9	12.02	-0.630	0.397	144.480
#10	9.25	-3.405	11.594	85.563
#11	13.85	+1.195	1.428	191.823
#12	11.75	-0.905	0.819	138.063
#13	9.60	-3.055	9.333	92.160
#14	9.60	-3.555	12.638	82.810
#15	20.00	+7.345	53.949	400.000
Total	189.820	0.000	309.361	2711.478

CALCULATION OF VARIANCE

$$\text{Variance} = s^2 = \sum_{i=1}^{N} X_i^2 - \frac{\left(\sum_{i=1}^{N} X\right)^2}{n} \Big/ (n-1)$$

Control Group Variance:

$$s^2 = \frac{2148.742 - \frac{31138.132}{15}}{15-1}$$

$$s^2 = \frac{2148.742 - 2075.876}{14}$$

$$s^2 = \frac{72.866}{14} = 5.205$$

TEST GROUP VARIANCE:

$$s^2 = \frac{2711.478 - \frac{36031.632}{15}}{15-1}$$

$$s^2 = \frac{2711.478 - 2402.109}{14}$$

$$s^2 = 22.098$$

CALCULATION OF THE POOLED VARIANCE (In preparation to "t" test) of statistical significance

$$s_p^2 = \frac{\sum X_i^2 - \frac{(\sum X)^2}{n}}{(n_1 - 1)} + \frac{\sum X^2 - \frac{(\sum X)^2}{n}}{(n_2 - 1)}$$

$s_p^2 = 22.098 + 5.205$

$s^2p = 27.303$

Degrees of Freedom Permitted:

$Df = (n-1)$

$Df = (15-1)$

$Df = 14$

"t" TEST OF STATISTICAL SIGNIFICANCE

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{s^2p \ (1/n_1 + 1/n_2)}}$$

$$t = \frac{12.655 - 11.764}{\sqrt{27.303 \ (2/15)}}$$

$$t = \frac{0.891}{1.908} = 0.4670$$

The range of significant figures with 14 degrees of freedom is (2.16 to 3.01). Therefore, statistical analysis by use of the "t" test demonstrates there is no statistical significance

between the test and control groups as to 17-Ketosteroid excretion/24 hrs.

VII. DISCUSSION

In reconsidering idiopathic premature baldness, as a whole, one may begin by discussion on the area of hair loss. As noted in this malady, the primary site of loss is in the frontal parietal region of the scalp. Of all areas of the scalp which endure stretching and trauma the frontal-parietal area is foremost. One may realize this simple fact by recalling when he puts on his hat or combs his hair; this area is the first part of the scalp contacted. Therefore, by the use of teleologic or deductive reasoning one may use these facets to begin discussion of the theoretical physical factors which may contribute to idiopathic premature baldness.

The physical contributions to baldness can be first observed at birth. For an example, it is a commonly known fact some babies are susceptible to hair loss over the frontal-parietal region following delivery. One may ask oneself whether this hair loss is due to pressure ischemia and the shearing action of delivery. If so, then one may fit this reasoning very nicely into Dorsy[6] and Szaaz's[24] theory of hair loss due to the pressure of hat bands and the shearing action of scalp muscle vestiges, respectively, in the action of frowning and facial expression. However, if birth trauma is the cause of temporary baldness through these physical factors, and is suffered by

the majority of infants, then why is not the majority of infants affected by baldness similarly?

Exhausting further the physical factors of premature baldness, one may explore Young's[26] theory. Young postulates scalp tension leads to reduction in the thickness of the soft tissues and interference with circulation, with consequent hair loss. He has correlated his observations with sustained facial expression and frowning. On this basis he noted a higher incidence of premature baldness in the more intelligent male. He explains these findings by the fact more intelligent males are engaged in endeavors which tend to keep him long hours at desk work or reading, in which many hours of frowning or sustained facial expression are utilized in study. This tension and sustained fixing of the scalp muscles reduces the thickness of the tissues and, consequently, leads to decreased blood flow and hair follicle degeneration. One may extend Young's theory to the recent reports of baldness occurring in women who use the "pony tail" type hair style. This hair style places a stretch on the frontal scalp due to the hair of this region being pulled back to a "gather" over the occipital region of the scalp. On the other hand, one would ponder, upon critically analyzing Young's theory, why women of higher intelligence who also parallel the desk work, concentration, and study of their fellow men workers no not suffer from baldness? Therefore, one,

as he reviews the build-up of evidence of premature baldness, cannot account entirely for the primary etiology as being due to physical factors alone.

One may turn to viewing the bodily hair, as a whole, in relationship to the scalp and its flucuations. In doing so, one will note Harris's[8] study. Harris noted baldness occurs more frequently in persons with a relatively heavy growth of terminal hair elsewhere on the body than in those with scanty terminal growth. With this thought in mind and the fact one does not see baldness in the prepuberal individual, we could begin to conceive hormonal actions as being causative; and that a hormonal action on the terminal hair would seem to act conversely on the scalp hair. This form of reasoning was defined more clearly by Albireux,[1] who found the terminal growth of hair on the body relative to puberty is made to increase with testosterone stimulation, while the converse is true with the frontal-parietal hair of the scalp.

Rony,[19] while investigating testosterone effects, found the hormone stimulated the sebaceous glands of the scalp, but did not stimulate the hair follicles. He concluded responses provoked by testosterone in the hair follicle and in the sebaceous glands are two distinct and different phenomena, one depending on regional characteristics inherent in the responding tissue,

and the other independent of such factors.

Following these developments many workers began discovering the intricasies of hormonal inter-relationship. It was realized by many that this source of information would fill the gaps in some postulations and discredit others.

Marato'-Manaro[15] and others found testosterone and estrogen actions to be antagonistic to each other. He found either hormone would depress the response of the body to the other. Marato'-Manaro's work was carried out using the comb of a cock for a test indicator. This method of qualitative bio-assay was somewhat crude, but nevertheless effective in the hands of a competent observer. His findings have been substantiated recently with more refined bio-assay methods.

Therefore, integrating these findings into our own study and noting the action of testosterone having a different effect on the body as opposed to estrogen; we can readily realize why premature baldness is not observed in the woman with no known organic disease. In further support of these views, Simpson,[22] Kenyon,[12] Kanter,[11] and others have noted premature baldness and other masculinizing features in the human female during the presence of masculinizing tumor, such as, the arrhenoblastoma.

The arrhenoblastoma produces androgenic substances, increasing

the excretion of 17-Ketosteroids, over-riding or depressing the action of estrogen, and causing general terminal hirsutism save for the frontal-parietal region of the scalp which begins to become alopecic. These features and symptoms are completely regressive with the surgical removal of the arrhenoblastoma. This finding would encourage, greatly, those individuals in the practical aspects of a possible therapy for the malady of baldness. A complete cure would be the arrest and return to normal homeostasis of the hair follicle.

Hamilton[7] found parietal-frontal baldness would appear in eunuchs, castrated prior to puberty and having a familial history of baldness, if testosterone was administered. This work is the first definite correlation of the hormonal and herediteric postulations of premature baldness.

Our interest in the problem, however, resolved from another postulation: Whether or not the testosterone levels and consequent urinary excretion of 17-Ketosteroids is increased in the prematurely bald individual as opposed to the non-bald. This does not discredit the work of Hamilton, but merely compliments and tends to refine the hormonal relationships to the problem. Our approach does not deny the herediteric aspects proposed by Osborn's[16] classic work and the work of Snyder,[23] but is designed to lend further proof that testosterone and androgens, in general, are the necessary inter-

mediates in the reaction of premature baldness as initiated by heredity. It is our concept in androgen intermediates drive to completion this reaction. However, is there any associated general increase in the androgen levels of the prematurely bald? This view was indirectly held even in Aristotle's day, with his observation and correlation of increased sexual promiscuity among those who were prematurely bald. Therefore, our thoughts on the matter were organized and twenty four hour urine specimens obtained in those individuals, who were prematurely bald and those who did not possess this quality.

As one surveys the data presented, it is apparent, statistically, there is no gross correlation as to the quantitative amount of 17-Ketosteroid excretion / 24 hrs. in the non-prematurely bald individual as to the prematurely bald.

All data now being presented, one may integrate the findings to more fully understand the patho-physiological mechanisms involved. Understanding is essential in the laying down of a possible route of therapy for this malady. One may begin to use the interactions of hormones in preventing or prolonging the effects of heredity from developing. However, in the study of this problem the school of individuals interested primarily in therapy utilized every fragment of information discovered in relationship to premature baldness. Much of the information

had been uncorrelated and unfounded, which led to many erroneous methods of treatment. We shall discuss this phase of the malady.

As stated, many methods of therapy for premature baldness have been instituted. One popular therapy, without apparent experimental foundation, was the external use of anterior hypophyseal extract. Lord[14] proved conclusively, by his experiments, anterior hypophyseal extract therapy for baldness was a worthless and unfounded procedure, and had no effect in restoring hair growth to bald areas. Shapiro[21], however, had apparent success in his series of three men and three women with premature baldness by the external use of estrogen cream. These six individuals had scalp hair loss and scaling ranging in duration from three to one hundred months. Shapiro treated these patients with the estrogen cream, applied externally over the afflected areas. He noted a prompt and consistent response to therapy in three to six weeks, in all individuals. No systemic effects from the estrogen was noted, such as gynecomastia or impotence in the male, or menstrual irregularities and breast tenderness in the female.

The study and treatment by Shapiro seems to be the only successful method against premature baldness to date. According to the literature he is, apparently, approaching the subject from the majority of viewpoints held in the patho-physiology of

premature baldness.

Instead of adding an exogenous antagonist, such as estrogen to the male, one may postulate substances that would decrease the testosterone production in the male. However, as one investigates this avenue of approach he is faced with the systemic effects caused by the internal decrease in testosterone. Therefore, the method of choice would be to quell the testosterone at its site of action, in our case the scalp. Noting Shapiro's approach to the problem, which very nicely quells the testosterone effect at the local site of action, and does not cause systemic effects. Until, further work is done in the field of hormonal surpressors Shapiro's approach to the problem seems superior at the moment.

The systemic side effects, over a long period of time, with hormonal products, must be weighed against the apparent cosmetic value.

Perhaps, even in cases where a hereditary cause for premature baldness is established, the inevitable may be prolonged. One may look upon treatment of a "natural thing" such as premature baldness as a somewhat frivolous therapy of a few; however, to a young lady this could be a catastrophe. Also, living in our present atomic age makes all of us susceptible to the side effects

of radiation, of which, alopecia is one. Many other annoying and cosmetically unattractive diseases such as alopecia areata and its consequent hair loss may benefit from these studies.

VIII. SUMMARY

The etiological aspects of Idiopathic Premature Baldness have been brought forth from many avenues of approach, both theoretical viewpoints and experimental data, respectively.

Until this time, the most logical correlation with this malady has been with herediteric evidence and a supportive non-quantitative hormonal postulation.

One undisclosed postulation, whether or not, there was more androgen produced, and consequent higher blood levels, in the idiopathic premature bald individual over the non-bald individual, therefore, if, there was more androgen substances produced then the urinary excretion of 17-Ketosteroids in turn would be elevated. With this line of reasoning in mind, the problem was organized so that it could be studied in the laboratory. The data obtained from this investigation ruled out gross evidence of an increase in urinary excretion of 17-Keto steroids in the prematurely bald individual as to those of the non-bald individual.

The work in this paper does not deny the integration of hormonal and herediteric aspects leading toward Idiopathic

Premature Baldness.

Further discussion was conducted as to the inter-relationships of the various hormonal components concerned with Idiopathic Premature Baldness. In this discussion various viewpoints and investigative evidence were analyzed in an attempt to correlate the proven components of this malady, and a possible insight into its treatment.

Exogenous hormones have had limited success in the therapy of Idiopathic Premature Baldness. It has been suggested further study into the use of hormone therapy may prove valuable, as to the cure of this malady and other related disease states.

IX. CONCLUSION

In concluding, it was found in Idiopathic Premature Baldness there is no related quantitative increase in the urinary excretion of 17-Ketosteroids. Therefore, one may extend this statement by suggesting idiopathic premature baldness is not accompanied by higher body levels of androgen than in the non-bald condition. On these findings one may conclude androgens are not the sole cause of Idiopathic Premature Baldness, but one of the intermediates needed to complete the reaction initiated by heredity. Therefore, at present, one must conclude the inherent predisposition toward premature baldness are provided by herediteric sources, developed and matured by the normal levels of androgen seen in the human male.

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