THE HORMONES AND ACNE VULGARIS

I. URINARY ASSAY FOR AND THERAPEUTIC USE OF ANDROGEN

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To even the casual observer it is apparent that acne vulgaris must have some basic relation to the endocrine glands. Much has been written regarding this relation, but no one has as yet shown what it is. Only a few worthy experimental studies attempting to explore this sector are recorded, although a much larger number of essays tell of the therapeutic uses of a number of glandular products. Almost every time a new extract is made available, it is given an early trial in the treatment of acne. None of these products thus far has seemed effective.

Several authors [1] have recorded their experiences with the use of androgen for acne. Their opinions as to its effectiveness have differed somewhat. Moreover, none of the reports has been on a sufficiently large number of patients to furnish evidence outweighing the uncertainties attached to results of treatment of a dermatosis marked by much spontaneous change. For this reason it was thought worth while to record the results of the use of an androgen [2] in a larger group of patients under controlled conditions and to make urinary assays of androgen for some of them. We attempted to overcome to some extent the known variable clinical factor by choosing when possible patients resistant to standard forms of therapy or patients whose acne was of long duration and chronic.

URINARY ASSAY

The forty-eight hour specimens of urine were measured, and 2,000 cc. was taken for extraction; if the sample measured less than that, water was added to make

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1. Hamilton, J. B.: Treatment of Sexual Underdevelopment with Synthetic Male Hormone Substance, Endocrinology **21**:649, 1937. Molitch, M.: Treatment of Acne Vulgaris with Testosterone Propionate, ibid. **23**:803, 1938. Templeton, H. J., and Truman, S. R.: Endocrine Therapy in Acne Vulgaris, California & West. Med. **48**:337, 1938.

2. The preparation used in these experiments was testosterone propionate (perandren, Ciba).

2 liters. Concentrated hydrochloric acid was added in a quantity equal to one-tenth the volume of urine used. The mixture was heated to the boiling point and boiled slowly for fifteen minutes. The solution was cooled in water at room temperature, filtered through a paper towel to remove a small quantity of dark precipitate and then extracted in a continuous extraction apparatus similar to that described by Gallagher and his co-workers.[3] The procedure differed in that chloroform was used as the solvent and hence the direction of the current of the solvent was with gravity instead of against it. Extraction was carried out for forty-eight hours. The chloroform was distilled off under reduced pressure and the residue leached with ether. Further purification and separation of the estrogen from the androgen were effected by the procedure of Gallagher and his associates. The assay was different.

The androgenic fraction was finally put up in 13 cc. of corn oil. Dilutions were made from this stock as follows: (1) full strength, or 100 per cent; (2) 80 per cent; (3) 60 per cent; (4) 40 per cent, and (5) 20 per cent. The assay was carried out on white leghorn chicks 1 day old. Three chicks received each of the aforementioned dilutions in a dose of 0.2 cc. daily for six days. The combs were examined on the seventh day, or twenty-four hours after the last injection. It had been found previously that injection of 20 micrograms daily produced a noticeable increase in the size of the comb, which is in agreement with the observation of Dorfman and Greulich.[4] With each assay, 15 chicks were given injections of 20 micrograms of crystalline androsterone in 0.2 cc. of corn oil daily for six days. Usually about 13 of the 15 gave a positive response and served as controls. Thus, of the aforementioned dilutions, the lowest concentration causing a positive response in 2 of 3 chicks was assumed to contain a daily dose of 20 micrograms. The positive reactions were read by visual inspection of the comb by two different persons, whose observations were found to agree remarkably well. To rule out personal interpretations, the readings were made without knowledge of what the chick had received. Evidence of a positive response was an increase in the size of the comb, in both height and width, and a deeper color due to increased vascularity.

RESULTS IN NORMAL SUBJECTS AND IN PATIENTS WITH ACNE VULGARIS

The values for our small series of controls were within the range found by other workers and agreed fairly well with those of Gallagher and his co-workers and with those of Callow.[5]

The values for our patients with acne fell in the lower part of the range for normal subjects. These results are somewhat different from

3. Gallagher, T. F.; Peterson, R. I.; Dorfman, R. I.; Kenyon, A. T., and Koch, F. C.: The Daily Urinary Excretion of Estrogenic and Androgenic Substances by Normal Men and Women, J. Clin. Investigation **16**:695, 1937.

4. Dorfman, R. I., and Greulich, W. W.: Response of Chick's Comb to Naturally Occurring Androgens and Estrogens, Yale J. Biol. & Med. **10**:79, 1937.

5. Callow, R. K.: The Significance of the Excretion of Sex Hormones in the Urine, Proc. Roy. Soc. Med. **31**:841, 1938.

those of Wile, Snow and Bradbury,[6] who found that subjects with acne on the average excrete slightly larger amounts of androgen in the urine than do normal controls. It is difficult to see why the discrepancy in these two sets of results exists. It may be that the cause lies in the use of different test birds. Wile and his co-workers used capons, whereas we used chicks. It is true that the more generally accepted method of assay utilizes capons and not chicks, but we were able to get values in agreement with accepted values with the latter birds. We used chicks because with them we could detect increased excretion of androgen when injections of an androgenic substance (testosterone propionate) were given the subject. This will be the subject of another report. Since the completion of our studies, Dorfman and Hamilton[7] have published their results in studies which utilized chicks as the test birds. They too were able to detect increased andro-

Daily Urinary Output of Androgen (mg.)

Sex	Normal Subjects	Sex	Patients with Acne
F	2.6	F	1.2
F	2.6	F	1.8
M	4.0	M	3.0
F	1.9	F	2.6
F	4.0	F	1.8
M	4.0	M	2.4
F	3.6	F	1.6
F	3.9	F	1.8
F	2.4	F	2.5
		M	1.5
		M	1.2

genic excretions after administration of an androgen. Capons, on the other hand, do not have this increased excretion. Apparently the different androgens do not behave alike when injected into different test subjects.

A group of 24 patients with acne were given intramuscular injections of sesame oil for at least two months. This preparation was the diluent for the androgen used in these studies, and these injections served as a control for the treatment with the androgen itself. One cubic centimeter of the oil was injected once weekly. There were no general reactions and little local reaction. Seven of the patients were improved more than 50 per cent. One had complete clearing of the

6. Wile, U. J.; Snow, J. S., and Bradbury, J. T.: Studies of Sex Hormones in Acne: II. Urinary Excretion of Androgenic and Estrogenic Substances, Arch. Dermat. & Syph. **39**:200 (Feb.) 1939.

7. Dorfman, R. I., and Hamilton, J. B.: Urinary Excretion of Androgenic Substances After Intramuscular and Oral Administration of Testosterone Propionate to Humans, J. Clin. Investigation **18**:67, 1939.

eruption. Two of the improved patients had severe cystic lesions which underwent involution and assumed the form of less conspicuous papules.

Forty-six patients with acne were treated with androgenic substance for a period of at least three months. Each patient received 10 mg. of testosterone propionate intramuscularly once a week. Twenty-four of this group were improved at least 50 per cent. In 9 the eruption cleared entirely. Of these, 5 relapsed two weeks to three months after the cessation of treatment. These 5 were given further injections of testosterone propionate. Three again improved, while 2 were refractory. Patients who received testosterone propionate and showed less than 50 per cent improvement had nothing peculiar about them to distinguish them as a group from those who fared better. Young women with acne of the chin responded poorly to this therapy. Patients exhibiting hard shotty papules did not do so well. When improvement resulted, the appearance was highly satisfactory. The deeper lesions on involuting left scarring and atrophy just as they do after any effective form of treatment.

SUMMARY

Patients with acne excrete quantities of androgen which lie at the lower part of the range for normal controls.

Forty-six patients with acne vulgaris were treated with androgen. Twenty-four improved somewhat, and in several the lesions cleared entirely.

Twenty-four patients with acne were treated with sesame oil only, the diluent material for the testosterone propionate used in the other group. Seven of these improved more than 50 per cent. One had complete clearing of the skin.