

NITROGEN RETENTION, CREATINURIA, AND OTHER EFFECTS OF THE TREATMENT OF SIMMONDS' DISEASE WITH METHYL TESTOSTERONE

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One of the immediate effects of hypophysectomy is a loss of nitrogen (1) and a corresponding loss in weight (2). This change is reflected clinically by the so-called cachexia of Simmonds' disease (3). Nitrogen balance is then re-established at a lower level of body weight with lessened food intake.

In the experimental animal, adequate replacement therapy is readily obtained with anterior hypophyseal substance or extracts (4, 5), including the production of nitrogen retention and gain in weight (1). Clinically, however, such attempts have been singularly unsuccessful (6, 35) except for one case treated with pregnant mare's serum (7), and another recent report by Williams (8), of treatment with a mixture of thyroid, desoxycorticosterone, and methyl testosterone.

The recent reports of growth in cases of dwarfism treated by methyl testosterone (9) reveal that nitrogen retention and creatinuria are produced. The origin of some types of dwarfism has been attributed by many to a disturbance in the growth function of the anterior hypophysis. This suggests that methyl testosterone may produce its effects on nitrogen metabolism in the absence of hypophyseal function, which is of great interest in view of the intimate role of the hypophysis in such metabolism (10). However, since the cause of the dwarfism cannot be definitely localized to the hypophysis (11), it would seem important to try methyl testosterone in cases of Simmonds' disease, in which hypophyseal function is known to be lacking and in which any effect on nitrogen metabolism is not complicated by concurrent growth. Positive results might well point to this hormone as a possible therapeutic agent in this disease.

Accordingly, a study was conducted in the

Presbyterian Hospital on two cases of Simmonds' disease due to destruction of the hypophysis by intrasellar tumors, a girl of 20 years and a man of 31. They were placed on a low creatine diet and balance studies were conducted before, during, and after treatment with methyl testosterone. Striking subjective, objective, and laboratory changes occurred. Two additional cases were treated and followed clinically, with the production of similar changes, although it was not possible to secure adequate laboratory data. These are mentioned briefly at the end of the text and their case histories are appended.

METHODS

The case histories of the 2 patients used in this study are detailed at the end of this paper. Both were placed on low creatine diets, the man receiving 2,450 calories per day composed of 290 grams of carbohydrate, 75 grams of protein, and 110 grams of fats; the girl received 1,600 calories divided into 200 C, 55 P, and 65 F, calculated from diet tables. The man carried on his customary activities; the girl was unable to do so, due to weakness, and remained in bed. All urine was pooled as 24-hour outputs under toluol, for analysis of total nitrogen, creatine, creatinine, uric acid, and phosphorus. Occasional 24-hour specimens were collected with chloroform for 17-ketosteroid determination. Nitrogen was determined by a modified micro-Kjeldahl method (12), creatine and creatinine by a modification of the Folin method (13), uric acid by the Brown method (14), and phosphorus by the Fiske and Subarrow method (15). Urinary 17-ketosteroids were determined colorimetrically by the Zimmermann procedure as detailed by Callow and Callow (16), following an extraction procedure previously outlined (17). Bloods for cholesterol, sugar, and serum protein partition were determined by the Bloor (18), Folin and Wu (19), and Howe (20), methods respectively. Basal metabolic rates were run in a closed system apparatus, using the DuBois formula for surface area calculations. Crystalline methyl testosterone,² 10 mgm. tablets each,

² Dr. Edward Henderson of the Schering Corporation generously supplied the methyl testosterone and the placebo tablets. Mr. Mautner of the Ciba Corporation furnished a small quantity of methyl testosterone, also.

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TABLE I

Table listing the urinary excretion values for nitrogen, creatine, creatinine, inorganic phosphorus, and uric acid in Simmonds' disease, before, during, and after methyl testosterone administration

Patient R. K., female, on a diet containing 8.8 grams of protein N per day, less 0.4 grams N in stool

Day of experiment. Start—April 21, 1942	Treatment	Nitrogen	Creatinine	Creatine	Phosphorus	Uric acid
		<i>grams per 24 hours</i>		<i>mgm. per 24 hours</i>		
1 to 7 8 to 15 16 to 22	Methyl testosterone	3.35 3.60 3.19	0.617 0.600 0.560	0.369 0.433 0.354	Average 0.460	Average 0.216
23 to 30 31 to 38 39 to 46 47 to 54 55 to 62	None	5.12 6.11 6.82 6.71 6.53	0.765 0.706 0.744 0.696 0.708	0.493 0.343 0.317 0.244 0.196	Average 0.620	Average 0.306
63 to 70 71 to 77	Methyl testosterone	4.47 4.26	0.693 0.700	0.202 0.357	Average 0.490	Average 0.282

Patient McA., male, on a diet containing 12.0 grams protein N per day, less 1.1 grams N in stool

Start—May 1, 1942 1 to 7 8 to 12	None	9.67 8.68	1.28 1.23	0.090 0.100	Average 0.680	Average 0.320
13 to 20 21 to 28 29 to 36 37 to 44 45 to 53	Methyl testosterone	7.35 7.81 8.53 9.68 9.07	1.27 1.36 1.40 1.45 1.50	0.111 0.091 0.192 0.330 0.313	Average 0.610	Average 0.400
54 to 61 62 to 69	None	9.42 11.23	1.52 1.51	0.269 0.296	Average 0.745	Average 0.342

were given in 20 mgm. doses, 5 times daily. Exact duplicate tablets without hormone were used as placebos during the control periods.

RESULTS

Clinical. Both patients had been carefully followed for 4 years prior to the present experiment, without any appreciable alteration in their condition during the past 2 years. Both complained of weakness and lack of energy. The girl was bed-ridden, whereas the man was able to carry out only desk work, though capable of strenuous manual labor prior to the onset of his disease. After several weeks of methyl testosterone administration, both patients manifested a sense of well-being, greater muscular strength, and an increase in appetite. The man, who had had only an occasional erection and no ejaculation for at least 4 years, spontaneously noted a return of normal frequency of erections and had several nocturnal emissions, as well as a definite sense of libido. The girl, interestingly, began to discuss her "boy friends" and displayed a degree of spontaneous

activity quite gratifying to all who had observed her previous lethargy. On identical appearing placebo tablets, this improvement persisted for a month and then disappeared.

Physical changes with treatment were definite. Secondary sex hair, which had completely disappeared in both, reappeared in the axillae and pubic regions after 3 or 4 weeks, and increased for several weeks after the introduction of placebos. However, no seborrhea appeared, unlike the almost invariable occurrence of this condition in eunuchoids so treated (21). Biceps tone and size apparently increased in both, though the element of enthusiastic cooperation on the part of the patients cannot be ruled out. The girl, however, in the latter part of the treatment was able to get out of bed and stand unassisted to be weighed, which she had not done for 2 years. Blood pressure remained essentially unaffected in both. The size of the prostate doubled to one-half adult size in the man, the testes were unaffected, and the uterus of the girl remained atrophic. Breast changes were borderline, if real, in both. Body

weight started to increase almost immediately, and continued to rise throughout the period of treatment, decreasing upon cessation of the drug. The subjects gained about 10 lbs. each during the limited period of treatment, the girl's weight increasing from 123 to 131 lbs., and the man's from 176 to 186 lbs.

Laboratory. Clear-cut changes occurred from the laboratory standpoint, also. The appearance of nitrogen retention and an increase in creatinuria were the most interesting, and are detailed below (Figures 1 and 2; (Table I). The basal metabolic rate tended to rise and the fasting serum cholesterol to fall, the cholesterol reaching unusually low levels for both (Table II). A slight rise in serum albumin and decline in globulin were suggested, but more data are needed. No change occurred in serum sodium, NPN, urinary 17-ketosteroid output, serum electrolyte partition including sodium, or in the complete blood count.

Oral glucose tolerance tests reverted to a normal pattern.

The composition of the diets was calculated from standard tables and was not analyzed. Stools were analyzed for nitrogen in both patients, with and without treatment, and the results in both periods were essentially the same. The urinary nitrogen output was about 3 grams greater daily in the woman without treatment than with it, and about 1 gram greater in the man. This difference was less toward the end of the treatment period in the latter. A loss of some of the retained nitrogen occurred in the man on stopping the drug. The administration of the drug decreased the wide daily fluctuations in nitrogen excretion.

A mild creatinuria was present during the control periods but became greatly exaggerated after 3 weeks of treatment. This slowly declined following cessation of the drug for about the same length of time. Renewal of therapy then raised

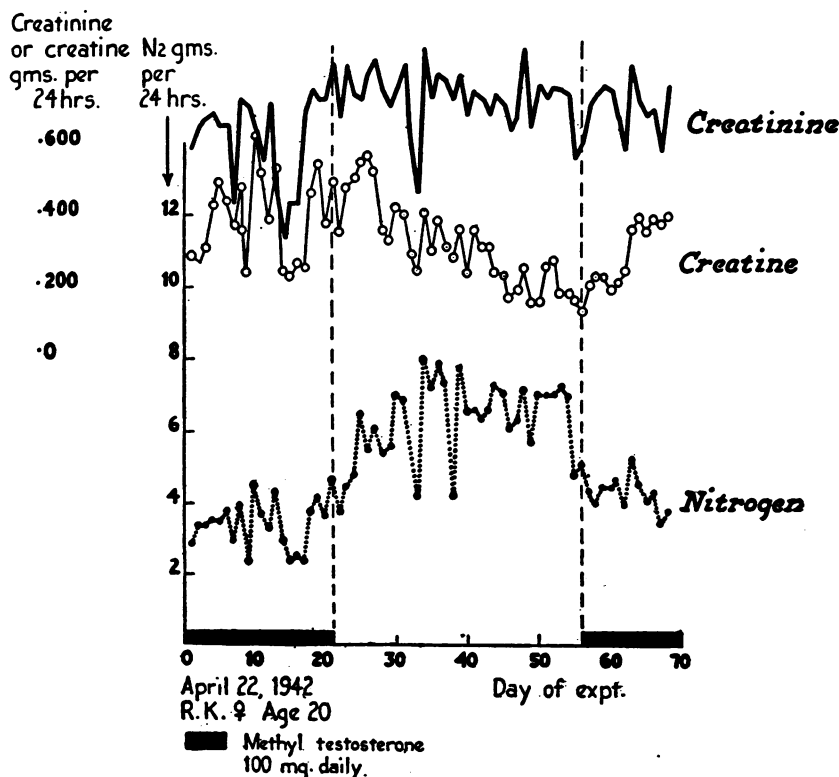


FIG. 1. GRAPH SHOWING THE EFFECT OF METHYL TESTOSTERONE THERAPY UPON THE URINARY EXCRETION OF NITROGEN, CREATINE, AND CREATININE OF PATIENT R. K., FEMALE, AGE 20, WITH SIMMONDS' DISEASE DUE TO AN INTRACRANIAL TUMOR

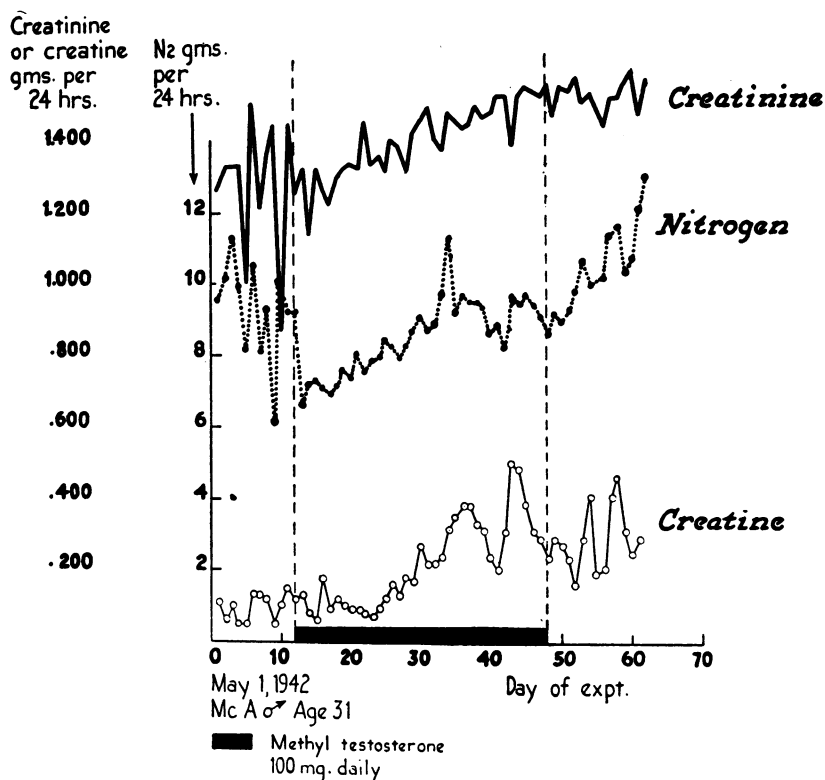


FIG. 2. GRAPH SHOWING THE EFFECT OF METHYL TESTOSTERONE THERAPY UPON THE URINARY EXCRETION OF NITROGEN, CREATINE, AND CREATININE OF PATIENT McA., MALE, AGE 31, WITH SIMMONDS' DISEASE DUE TO A PITUITARY ADENOMA

TABLE II

Table showing the effect of methyl testosterone administration upon basal metabolic rate and fasting serum cholesterol in Simmonds' disease

McA.				R. K.				E. S.			
Treatment	Date	Basal metabolic rate	Fasting serum cholesterol	Treatment	Date	Basal metabolic rate	Fasting serum cholesterol	Treatment	Date	Basal metabolic rate	Fasting serum cholesterol
None	April 7, 1942	-34	mgm. per cent 187	None	March 20, 1942	-28	mgm. per cent 255	None	April 7, 1942	-40	mgm. per cent 328
	April 30, 1942	-41			April 8, 1942	-33		Methyl testosterone	June 2, 1942	-23	288
	May 12, 1942	-36	204	Methyl testosterone	April 16, 1942	-46		None	July 21, 1942	-23	361
Methyl testosterone	June 11, 1942	-32	134	March 28, 1942 to May 13, 1942	April 23, 1942	-37	290	W. L. G.			
May 12, 1942 to June 17, 1942	June 17, 1942		107		April 30, 1942	-37		None	October 21, 1941	-24	268
None	June 22, 1942	-41	94		May 8, 1942	-21		Methyl testosterone	June 15, 1942	-12	274
	June 24, 1942		125		May 13, 1942	-26		February 28, 1942, to June 15, 1942			
	July 1, 1942	-39	148	None	May 25, 1942	-35					
				Methyl testosterone June 18, 1942 to June 30, 1942	June 19, 1942	-32					
					June 23, 1942	-37	230				
					June 25, 1942	-32					
					June 26, 1942	-30	194				
					June 30, 1942	-28					

the output to its previous high levels, much more quickly. Uric acid excretion showed no definite correlation with the other values. Inorganic phosphate output tended to follow nitrogen. The creatinine excretion was inconsistent, inasmuch as it tended to rise during treatment in the man, and after treatment in the woman.

COMMENT

The effects of replacement therapy in the hypophysectomized rat, treated with anterior hypophyseal implants and extracts, are well known (2). Nitrogen retention occurs with little change in the other urinary constituents, except salts and phosphorus which parallel nitrogen output (1). Likewise, the extremely important role played by the anterior hypophysis in the regulation of nitrogen metabolism as it relates to protein storage and breakdown in the intact animal has been made progressively clearer (22). The fact that methyl testosterone will cause nitrogen retention, and hence presumably protein synthesis, during markedly reduced or possibly absent hypophyseal function, just as it does in the normal and in eunuchoidism (23), would tend to indicate that the fundamental mechanisms involved in nitrogen metabolism may be influenced in the absence of the hypophysis. This is also indicated by the fact that when nutrition is forcibly maintained at its previous level, weight loss may be prevented with maintenance of body nitrogen, despite the other manifestations of anterior hypophyseal lack (24).

Two alternative and less likely possibilities present themselves. It is possible that methyl testosterone may activate remaining hypophyseal tissue to an increased degree of function. The failure of 17-ketosteroids to rise in the urine is against this. The sole source of these urinary steroids in women is the adrenal cortex, as shown by the disappearance of these substances consequent to the destruction of the adrenal in Addison's disease (25). In men, an additional fraction is derived from the testes due to the conversion of testosterone in the liver (26). Since the secretory activity of both the adrenal cortex and of the testis is largely dependent upon the anterior hypophysis (2), failure of the latter results in the disappearance of 17-ketosteroids from the urine of both sexes. Renewed adrenotropic or, in the male, gonadotropic

activity under these circumstances might be expected to cause a re-rise in steroid output. Thus the failure of the cases under discussion to demonstrate such a rise is evidence against increased hypophyseal activity. Since testosterone has a gonadotropic action in maintaining spermatogenesis in the hypophysectomized animal (27), another possibility is that methyl testosterone may imitate other hypophyseal hormonal effects, namely, upon nitrogen metabolism.

The effect on creatine metabolism is of a degree which indicates a specific action of the hormone. Transmethylation (28) alone, with the utilization of all the methyl groups contained in the 100 mgm. of methyl testosterone for the synthesis of creatine, would account for only 135 mgm. if used solely for this purpose. The 400 mgm. levels of excretion attained by the patients studied here, and an output of 1,200 mgm. in 24 hours in a eunuchoid on this dosage (29), show the reaction to be beyond the amounts accounted for by the possibility of transmethylation.

The effects on basal metabolic rate and cholesterol are similar to those reported in eunuchoidism treated with methyl testosterone (30). The mechanism and significance of these changes is unexplained.

The failure of seborrhea or folliculitis to develop, despite secondary sexual hair growth in these and in the other 2 cases with this condition similarly treated, is important. These manifestations occur almost universally in eunuchoids so treated (21). It thus appears likely that certain basic conditions are necessary before androgens can act upon the skin to produce seborrhea. This fundamental preparation of the skin is lacking as a direct, or indirect consequence of the hypophyseal failure. Hamilton (31) has quantitated sebum secretion with a fluorescent light after ether extraction of the skin, but these methods have not as yet been employed in the cases presented in this study.

The growth of secondary sex hair is interesting in view of the absence of adrenal androgens, both before and during therapy, as revealed by the 17-ketosteroid excretion. The effect of the methyl testosterone on the man's genital tract corresponds to the effectiveness of the hormone in the hypophysectomized animal (32). This is not true of

the woman since the uterus failed to respond (33). Matters of dosage and length of administration may enter into this.

The striking clinical improvement consequent to treatment merits a word of comment. Sense of strength and well-being are indefinables which cannot be measured. However, one's experience with these patients tends to lend weight to the response noted here, a result which has failed to materialize with the use of many other therapeutic agents. How long the hormone will continue to be effective is being observed. Libido has persisted in the 2 patients not included in this study, for the past 6 months, with progressive weight gain during this time, while on the drug.

The question of whether hypophyseal function is entirely absent in these cases is a cogent one. In the rat, the removal of nine-tenths of the gland produces no symptoms (2), but beyond this, the whole picture of insufficiency may develop despite remaining fragments of the gland. Thus, these patients may have small amounts of functioning tissue even though the clinical picture of hypophysectomy is complete,—namely, pallor, asthenia, total loss of secondary sex hair, loss of genital function, no 17-ketosteroid excretion, and low basal metabolic rate. As for weight loss, the man was well below his former average weight of 205 lbs., but the girl was force-fed at home and was slightly obese. However, recent experience has shown that mild obesity may be present despite complete destruction of the anterior hypophysis, proven at autopsy (34). There is one feature in the girl which suggests possible hypophyseal activity, namely, a slight but definite increase in the size of the thyroid gland over the past few years. However, her basal rate remains — 40 per cent.³

Clinical results from the treatment of 2 other men with anterior hypopituitarism due to tumor were obtained during this study. The results, as far as libido, weight gain, and sense of well-being, have been as striking as in the cases reported here. Likewise, seborrhea failed to appear, as mentioned above, although growth of secondary sex characteristics occurred. Laboratory data are insufficient for presentation. Their case histories are appended.

³ Subsequent autopsy failed to reveal any pituitary cells whatsoever.

SUMMARY

Striking subjective, objective, and laboratory changes followed the treatment with methyl testosterone of 4 patients with Simmonds' disease.

Clinically, the patients demonstrated renewed vigor, sense of strength and libido, and redeveloped secondary sex characteristics.

Seborrhea failed to appear, suggesting that androgens act to produce seborrhea only after the skin has been prepared by some basic mechanism or mechanisms, which are wanting following hypophyseal failure.

In the absence of hypophyseal function, the administration of methyl testosterone resulted in nitrogen retention, associated with persistent weight gain.

Marked creatinuria developed after a latent period of several weeks, and subsided in about the same length of time after stopping treatment.

The therapeutic value of methyl testosterone in Simmonds' disease or anterior pituitary insufficiency is suggested by the cases in this series. A more extensive clinical trial of the drug is warranted, and more clinical and laboratory data should be accumulated.

The authors are indebted to Miss Genevieve Corbett and to Miss Elizabeth Zabriskie for technical assistance.

CASE HISTORIES

Case 1. R. K. P. H. Unit No. 497847. Female. Single. Age 20 years.

The complete history to 1940 has been previously summarized (35). The diagnosis of aneurysm of the internal carotid artery within the skull was made, and wiring with electrothermic coagulation was performed in 1938, following the failure of bilateral ligation of the carotid arteries in the neck to halt the destruction within the skull. A true picture of advanced hypopituitarism, or Simmonds' disease, was present, due to the progressive destruction of the sella turcica and its contents. During the 2 years from 1938 to 1940, no further change within the skull occurred. There was some alleviation of the Simmonds' picture. A weight gain of 20 lbs. followed intensive feeding at home. A suggestion of pubic and axillary hair growth, and a glucose tolerance curve which tended to be diabetic in character, rather than the earlier flat curve, were noted. Urinary 17-ketosteroids remained zero.

In May 1941, a new set of symptoms appeared, consisting of spells of confused consciousness, preceded by flashes of light, incontinence, and alternate flushing and blanching of the face. There were no convulsive movements. The attacks lasted several minutes. They came

irregularly, from several hours to several weeks apart. Fasting blood sugars during the attacks were 90 to 100 mgm. per cent. An electroencephalogram revealed a "pathological picture consistent with a number of pathological states including cerebral anemia plus a destructive lesion in the right frontal and temporal regions." These alterations have persisted to the present.

In November 1941, the patient was readmitted for the 11th time, because of 3 months of mild diarrhea which soon cleared.

Physical examination: Her blood pressure was 80/60. Her striking facial pallor was unchanged. The angles of the mouth showed fissuring, redness, and erosion of the skin. A slight suggestion of pubic and axillary hair was noted. Her status otherwise was unchanged from previous occasions. A neurological examination revealed a left lower facial palsy, hypesthesia of the right side of tongue and face, a right 5th motor weakness, and a deviation of the tongue to the left.

Laboratory: The essential finding on this admission was in the x-ray of skull. This revealed a remarkable increase in the destruction of the skull as compared to the films of 1 year before. The wire previously inserted, was displaced posteriorly, the base of the skull was further damaged, the lateral wall and roof of the right orbit were further eroded, and the left optic canal was now 1 cm. in diameter. Several urine specimens showed a creatine of 0.09 gram and creatinine of 1.113 grams per 24 hours.

Course: The increased destruction of the skull in the face of the wiring, suggested the possibility that a tumor such as a chordoma, instead of an aneurysm, might be present, though Drs. Pfeiffer and Dyke felt the x-ray picture was still consistent with one, or several, aneurysms. The patient was essentially bedridden. She remained *in status quo* until her next admission for methyl testosterone therapy.

12th admission, Presbyterian Hospital, Ward H Met.
March 20 to June 6, 1942. Age 20.

The history and physical examinations were unchanged. Her weight was 123½ lbs.

Laboratory: X-rays of skull were unchanged since 4 months previously. Dr. C. Dyke of the Neurological Institute believed an aneurysm of the right side of the circle of Willis was still the most likely possibility.

Course: The patient was started on methyl testosterone, 20 mgm., 5 times a day, by mouth, batch no. 1LL 17 of Schering's Oreton—M, 1 week after admission, to see the effect on her weakness. Several urinary creatines were done 1 to 2 weeks after starting therapy, and indicated that a definite increase had occurred. A gain in weight of 8 lbs. was noted and suggested the possibility of either water, fat, or nitrogen retention. Accordingly, a balance study was planned, and the results are shown in the figures and tables. Data concerning other laboratory findings are listed in Table II. Methyl testosterone therapy was continued until an unquestionable clinical improvement was noted by all, a month after starting treatment. The patient sat unassisted. A slight bladder dribbling ceased. She became alert, interested in her surroundings, and slept

less. No seborrhea was noted, though, by May 11th, pubic and axillary hair were definitely growing, and fine hairs were visible over abdomen, chest, and upper lip. Her weight fell but re-rose to 131½ lbs. No uterus was palpable on gynecological examination. On May 13, the patient was started on placebo tablets without hormone, batch no. 2SP1. No especial change occurred for 5 days. Then the patient had her first central nervous system attack in several months. From this point on, the patient slowly declined to her initial state of inactivity. By June 18th, she had lost all ground previously gained. She was recommenced on methyl testosterone, batch no. 2LL3. A weight gain of several pounds occurred again. The experiment was halted June 20th, however, because of the increasing severity of her central nervous system attacks. Serum protein values done on entry showed a total of 7.5 per cent, albumin 4.7 per cent, and globulin 2.8 per cent, and did not change during therapy.

Autopsy on October 11, 1942, showed an aneurysm of the internal carotid artery, posterior communicating branch, with no demonstrable pituitary tissue either on gross or microscopic examination. Death followed an intracranial exploration. This procedure was a last resort measure to attempt to control the increasing central nervous system involvement.

Case 2. A. McA. P. H. Unit No. 555816. Single.
Male. Age 31 years.

The patient was first admitted to the Neurological Institute in October 1932, at the age of 21, because of headache, diplopia, and loss of all vision but light in the left eye, for the past year. This followed 3 years of increasing size of head, hands, and feet. There had always been some prognathism. The main findings on physical examination revealed early acromegalic features, generalized weakness, a temporal visual field defect in the right eye, and only upper left quadrant vision remaining in the left. His height was 6 feet and 1 inch, and weight 195 lbs. Laboratory work-up revealed a distorted sella consistent with a slow-growing tumor; overgrown sinuses and prognathism of the jaw consistent with acromegaly; and x-rays of the feet showing tufting of the terminal phalanges.

Course: He was given an intensive course of radiotherapy, 1,500 r. Only slight bitemporal hemianopia remained on discharge. He then received a second course of 1,500 r. following discharge from the hospital.

In October 1938, he was admitted to the metabolism ward for study. There was a family history of the mother having died of lymphatic leukemia. Physical examination revealed rheumatic fever in childhood without sequelae. He had had Autumn hay fever since he was 6; a T. & A. in childhood; a bone cyst removed from the left femur in 1934. He now complained of weakness, weight loss from 214 lbs. 5 years ago, down to 180 lbs. at present, and loss of libido and potency except for rare erections. Nocturnal emissions had ceased. He also complained of "anemia," *i.e.*, marked pallor of the face. Physical examination revealed a typical acromegalic with a marked pallor of the face. There was no facial, axil-

lary, or pubic hair. The left optic nerve was pale. He shaved 3 times a week. He had fainted 3 times in the last year. Shoe size had decreased, since 1932, from 10 to 9, and shoes from 11E to 10½D; hat size from 7½ to 7¼. He was bothered by the cold and tired too readily. His blood pressure was 92/70. The testes were normal in size but soft and mushy. The prostate was impalpable. There was a scoliosis of the thoracic spine to the left.

Laboratory: The hemoglobin was 14.5 grams; red blood cells 4.86 million; white blood cells and differential normal. Fasting serum cholesterol 178 mgm. per cent. Calculated serum sodium 137.1 m.eq. Blood NPN 32 mgm. per cent. Glucose tolerance tests on 2 occasions, with 100 grams of glucose orally, were similar. Fasting 68 mgm. per cent, ½ hour 60 mgm. per cent, not rising above 80 mgm. per cent. Kline blood test negative.

Course: The patient was followed in the clinic with little change. He was readmitted in April 1942 for a trial on methyl testosterone.

2d Admission, Ward G Met. April 30 to July 7, 1942.

The chief symptoms were still muscle weakness, inability to lift heavy objects or run up a flight of stairs, dyspnea on 2 flights of stairs, and constant sense of fatigue. He shaved once a week. There had been no ejaculation since the onset of the present illness though an erection occurred about once a week. There was no libido. Cramps in the muscles of the fingers and hands had been present for the past 7 to 8 months.

Physical examination was unchanged from the last admission and the blood pressure varied between 90/65 to 100/70.

Laboratory: Basal metabolic rate was 36 per cent. X-ray of skull unchanged. Fasting serum cholesterol 204 mgm. per cent. Blood sugar 83 mgm. per cent. Blood NPN 26 mgm. per cent. Calculated serum sodium 142.8 m.eq. Serum proteins 6.4 per cent with albumin 4.4 per cent and globulin 2.0 per cent.

Course: The patient was observed for 2 weeks without any therapy. During this period, he left the hospital between 9:30 a.m. and 5:00 p.m. to go to work, taking lunch with him from the hospital. He saved his urine during this time also. He was then given methyl testosterone, 20 mgm. 5 times a day, continuing the same regime of work and diet, etc. Within 2 weeks, he noted increased ability to work and walk stairs, and noted much less fatigue. There was a return of libido and an increase in the frequency of erections. After a month of therapy (June 17), the prostate had increased to ½ normal adult size. Pubic and axillary hair were growing, but no seborrhea was noted. Laboratory findings are recorded in Figure 1 and in Tables I and II. The serum protein was 6.2 per cent with albumin 4.6 per cent, globulin 1.6 per cent. For the last 2 weeks of the experiment, the patient was then started on an identical placebo pill without subjective change, except for some decline in strength. Three months after leaving the hospital, December 19, 1942, while taking methyl testosterone, 10 mgm. 5 times a day, he had gained up to 205 lbs., felt "the best he ever

felt in his life," and contemplated marriage. No seborrhea was noted though hair growth continued. The prostate was unchanged.

Case 3. W. L. G. P. P. Married. Male. Age 39 years. (Referred through the courtesy of Dr. Paul Sheldon.)

This patient was first seen in October 1941, because of declining sexual potency for the past two years. Family history revealed the mother to have had diabetes for years. His past history was essentially non-contributory except for a tonsillectomy at 10 and an operation for a deviated nasal septum at 20. The patient had eaten a peculiar vegetarian diet between the ages of 13 and 25. He felt the diet had insufficient protein. However, he underwent a normal puberty from 16 to 18 and had a normal sex life including marriage at 27 years of age. There were no pregnancies despite efforts. At 25 years of age, the patient developed a persistent anemia, later diagnosed "pernicious anemia," for which he had been taking feosol, thyroid, and liver, to the present. Two years before being seen here, the patient had been to Mexico where he had a diarrhea which cleared shortly, although his stools were said to continue to show an excess of fat. About this time, there was a sudden loss of libido with a loss of hair over the body, axillary, and pubic regions. After a year and a half, there was a sudden loss of vision in the right eye, without headache or vomiting. Libido declined to the point where his wife threatened a divorce. His weight had fallen 20 lbs., to 155 lbs. There was a continuous lack of energy. Physical examination revealed a very pale man without sexual hair, a prostate that could barely be made out, slightly soft testes, and eye defects described by Dr. Truman Boyes: "An absolute right central and paracentral scotoma, a constriction of the superior nasal field of the right eye and nasally of the left eye." The rest of the examination was negative. B.P. 110/70.

Laboratory: Hemoglobin was 14.1 grams; red blood cells 4.4 million; white blood cells 6,000 with 49 polymorphonuclear cells. The basal metabolic rate was 24 per cent. Fasting serum cholesterol was 267 mgm. per cent. X-ray of skull (Dr. C. Dyke) showed a large pituitary fossa, with large frontal sinuses and thinning of the dorsum sellae consistent with an adenoma. Glucose tolerance curve, with 100 grams glucose orally, showed only a slight rise and fall over 3 hours.

Course: The patient was started on sublingual testosterone in propylene glycol and 10 per cent alcohol (36), 15 mgm. 3 times a day, from December 13 to February 28, 1942, without appreciable change. On February 28, methyl testosterone, 10 mgm. 3 times a day by mouth, was started. Within 3 weeks the patient complained of too frequent erections. He had gained 4 lbs. He was continued on this dosage, except for 1 month on 20 mgm. 5 times a day. By June 15, hair was growing on face, pubis, and axillae. The basal metabolic rate was 12 per cent. Fasting serum cholesterol 274 mgm. per cent. The patient was then returned to 10 mgm. 3 times a day August 5, 1942. The patient stated in a letter "I'm in

blooming good health, everyone says I look better than I ever have, and I now weigh 170 lbs."

Case 4. E. S. P. H. Unit No. 544056. Male. Married. Age 63 years.

This patient was 63 years old at the time of the present experiment. He had been seen in the Neurological Institute, Presbyterian Hospital, and Vanderbilt Clinic since April 1928 because of an adenoma of the anterior lobe of the pituitary with hypopituitarism.

On first admission to the Neurological Institute, April 12 to April 29, 1938, his chief complaint was blurred vision for one year. The family history was irrelevant. His past history revealed August hay fever for years, fractured left leg 9 years ago, pneumonia 5 years ago, varicose veins and hemorrhoids 5 years ago, and small gonads since puberty, though no disturbance in sexual function had been noted till 5 years ago, when impotence developed. His present illness began 1 year before admission with headaches and progressive visual disturbances, including diplopia and loss of temporal vision. Physical examination revealed a Fröhlich type individual with scant beard, female escutcheon, fat breasts and small genitals, the testes being approximately $1 \times 1 \times 1$ cm. The only other positive findings were pallor of the optic discs and bi-temporal hemianopia. The blood pressure was 136/80.

Laboratory: The basal metabolic rate was 23 per cent. X-rays of the skull showed enlargement of the sella turcica with atrophy of the posterior clinoids and dorsum sellae. X-rays of the optic foramina revealed bilateral atrophy consistent with a pituitary adenoma (Dr. C. Dyke).

Course: The patient received 7 x-ray treatments with some improvement in the visual fields. Subsequently, the patient had a series of admissions to the Presbyterian Hospital and the Neurological Institute. First admission to the Presbyterian Hospital, June 3 to 23, 1938, was for lobar pneumonia RLL, organism undetermined. At this time, the diagnoses of multiple left renal calculi, prostatic calculi, and cystitis were made. The patient was then transferred to the Neurological Institute from June 29 to August 25, 1938, because of progressive loss of vision. After a second course of x-ray therapy, a right frontal craniotomy with removal of most of a large pituitary adenoma was performed by Dr. C. Masson, July 21, 1938. A third course of radiotherapy was given shortly after discharge from the Hospital.

Subsequent events were the following admissions to the Presbyterian Hospital: September 13 to October 6, 1938, for chronic pneumonitis and asthma; April 3 to 20, 1939, for an acute right mastoiditis due to hemolytic streptococcus for which a simple right mastoidectomy was performed. Erysipelas developed in the wound but patient recovered uneventfully after this. A circumcision for phimosis was performed January 13, 1941. From October 16 to November 9, 1941, the patient was admitted to the G. U. service, for a left nephrectomy for renal calculus and an infected hydronephrosis. In December 1941, the patient bumped the unprotected area of his head. He de-

veloped mental derangement for a few days, requiring admission to the Manhattan State Hospital.

On April 6, 1942, patient was seen in the Vanderbilt Clinic regarding admission during methyl testosterone therapy. He refused admission but was willing to be followed in the O. P. D. At that time, he weighed 152 lbs., had been without erections for 10 years, felt tired, weak, and below par, but could work as a doorman. Examination showed marked pallor of skin, a few axillary and pubic hairs, small penis and retractile testes $1 \times 1 \times 1$ cm., but was otherwise negative.

Laboratory features are recorded in the tables. On April 20, methyl testosterone, 10 mgm. 5 times a day, was started. When next seen, June 2, he had frequent erections, definite libido, "felt better, stronger" than in years. On examination, the penis was larger, pubic and axillary hair was growing, and hair was appearing about nipples. The serum cholesterol had fallen and basal metabolic rate had risen. Urinary 17-ketosteroids were unchanged (Table II). Methyl testosterone was stopped, and the patient was not seen until July 21. At that time he wished to restart the drug because of decline in well-being. He was restarted on methyl testosterone 10 mgm. 5 times a day. On September 23, he stated he was the "best he had been in years." He now weighed 184 lbs. and boasted of his ability to "sling trunks," which he had been unable to do before. Sexually, his improvement was maintained.

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