December 5, 1963

THE PHARMACOLOGICAL USE OF ANABOLIC STEROIDS

Case [redacted] Agnogenic Myeloid Metaplasia

This 68 year old man was first admitted to the [redacted] in [redacted] of 1960 with a twelve month history of intermittent pruritis, headache, confusion, disorientation, and angina. Physical examination revealed an elderly plethoric man with engorged retinal veins and a palpable spleen. Admission laboratory studies revealed a Hgb. of 18.0, Hct of 70, WBC of 26,500, a uric acid of 9 mgm percent, and an incomplete left bundle branch block. Following phlebotomy of 500 cc the sensorium cleared, and the EKG returned to normal. A second phlebotomy was performed, and he was discharged (Hct 56) on 2 mg myeleran bid to be followed in the Parkland hematology clinic. The myeleran was discontinued approximately two weeks later (WBC 5,000 and Hgb 14.5 gm).

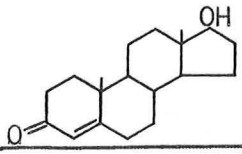
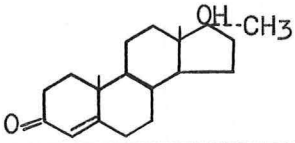
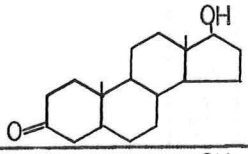
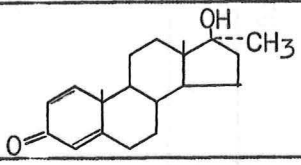
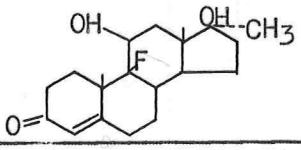
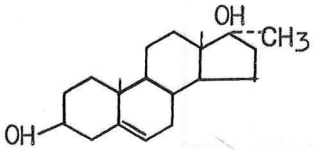
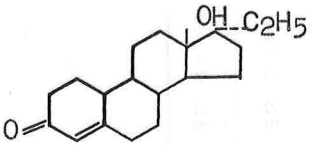
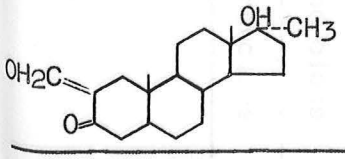
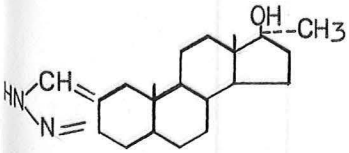
During the next two years the hemoglobin and hematocrit remained stable at around 14-15 and 40. He was admitted five times to the [redacted] and to [redacted] because of episodes of confusion and disorientation without localizing signs, thought to be due to arterial insufficiency.

By early 1963 he was noted to have lost weight; progressive enlargement of the spleen and liver were documented in successive visits to the outpatient clinic, and the hemoglobin and hematocrit fell (detailed below). Anisocytosis, poikilocytosis, nucleated RBC, and occasional myeloblasts were present in the peripheral smear. The leukocyte alkaline phosphatase was elevated to 172, and repeated attempts at bone marrow aspiration were unsuccessful. Bone marrow needle biopsy in May revealed predominantly fibrous tissue with megakaryocytic hyperplasia, sheets of platelets, and a paucity of red blood cell and white blood cell precursors. These findings were all interpreted as compatible with agnogenic myeloid metaplasia developing in the wake of polycythemia vera.

Testosterone propionate (10 mgm qid sublingually) was started on May 23. There has been no change in the size of the liver or spleen.

Date	Testosterone Therapy	Hematocrit	WBC	Platelets	Weight
[redacted]-62		40.5	17.7	100,500	135
[redacted]-63		37.0			
[redacted]-63		37.5	9.0		
[redacted]-63		32.0	20.5	227,500	111
[redacted]-63	+	36.5	24.5		
[redacted]-63	+	40	14.8	252,000	
[redacted]-63	+	46.0	35.6		
[redacted]-63	+	46.5	32.6		128

ANABOLIC STEROIDS IN CURRENT USE

Formula	Chemical Name	Trade Names
	Testosterone Testosterone-17-propionate	Multiple Names Multiple Names
	17α-methyltestosterone	Methandren, etc. (Upjohn and others)
	4-dihydrotestosterone	Stanolone
	Δ^1-17α-methyltestosterone (Δ^1-methyltestosterone)	Dianabol (Ciba)
	9-fluoro-11-OH,17-methyltestosterone (fluoxymesterone)	Halotestin (Upjohn)
	methylandrostenediol	Methandriol Crestabolic Mestenediol Metacryst Metandiol, etc. (several companies)
	17α-ethyl-19-nortestosterone 17α-ethyl-19-nortestosterone-17-phenylpropionate	Nandrolone Nilevar Norethandrolone Durabolin (Searle)
	2-OHmethylene-17αmethyl-17βOH-3 androstanone (oxymethalone)	Adroyd Anadrol (Syntex)
	Stanozolol	Winstrol

COMPARISON OF THE PROPERTIES OF CURRENTLY USED ANABOLIC STEROIDS

Name	Mode of Administration	Usual Daily Dose	Potency Relative to Testosterone		Side Effects
			Anabolic	Androgenic	
Testosterone	Buccal Intramuscular	5-25 mg. 10-75 mg.	100	100	Virilism; acne vulgaris; edema; flushing; priapism; testicular inhibition (azospermia); premature closure of epiphyses
Testosterone propionate	Intramuscular	10-75 mg.	100	100	Same as testosterone
Dihydrotestosterone	Intramuscular	50-100 mg.	75	75	Same as testosterone
Methyltestosterone	Oral Sublingual	10-40 mg. 5-20 mg.	100	100	Same as testosterone plus jaundice
Fluoxymesterone	Oral	2-10 mg.			Same as testosterone
Nandrolone	Oral	30-100 mg.	100	40	Same as testosterone plus BSP retention, edema, nausea
Durabolin	Intramuscular	25-50 mg.	100	40	Same as Nandrolone
Methylandrostenediol	Oral, Buccal, Sublingual, Intramuscular	10-40 mg.	80	68	Same as Nandrolone
Δ^1-methyltestosterone	Oral	5-10 mg. (1.25-2.5 mg.)	89	20	Same as Nandrolone
Oxymethalone	Oral	5-15 mg.			Same as Nandrolone
Stanozolol	Oral	6 mg.			Same as Nandrolone

REFERENCES

THE ANABOLIC EFFECT OF TESTOSTERONE IN DOGS

1. Kochakian, C. D., and J. R. Murlin. The effect of male hormone on the protein and energy metabolism of castrate dogs. J. Nutrition 10:437, 1935.

2. Kochakian, C. D., and J. R. Murlin. The relationship of the synthetic male hormone, androsterdion, to the protein and energy metabolism of castrate dogs, and the protein metabolism of a nor al dog. Am. J. Physiol. 117:642, 1936.

3. Kochakian, C. D. Testosterone and testosterone acetate and the protein and energy metabolism of castrate dogs. Endocrinology 21:750, 1937.

These three papers demonstrated that within 24 hours after the injection of "male hormone", the negative nitrogen balance of the castrated dog is reversed. After reaching a maximum (about 0.05 gm of nitrogen stored per kilogram per day) further injections only maintained the decreased nitrogen excretion at this level for the duration of the studies. Furthermore, this positive nitrogen balance occurred in the absence of any effect on energy metabolism in the castrated dog.

THE ANABOLIC EFFECT OF TESTOSTERONE IN MAN

4. Eidelsberg, J., M. Bruger, and M. Lipkin. Some metabolic effects of testosterone implants. J. Clin. Endocrinol. 2:329, 1942.

5. Kenyon, A. T., K. Knowlton, I. Sandiford, F. C. Koch, and G. Lotwin. A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. Endocrinology 26:26, 1940.

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7. Abels, J. C., W. F. Young, and H. C. Taylor. Effects of testosterone and of testosterone propionate on protein formation in man. J. Clin. Endocrinol. 4:198, 1944.

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13. Kochakian, C. D. The protein anabolic effects of steroid hormones. Vitamins and Hormones 4:255, 1956.

These papers represent the fundamental studies of the effects of testosterone derivatives on nitrogen balance in man. Testosterone-propionate produces a reduction in the urinary excretion of nitrogen, sodium, potassium, and chloride together with a gain in weight (in castrates only). The maximal nitrogen retention (0.03 gm. per kg. per day) in the normal men was half that of the eunuchoid men, and normal men under balance conditions do not gain weight. The positive nitrogen balance also occurs in elderly men, in patients with carcinoma, in patients with Cushings Disease and Addison's Disease, in nephrosis (accompanied by an increase in edema and proteinuria), in cachectic individuals, and in a variety of debilitated states. The positive balance can be reversed by any minor stress (such as a cold) and is short-lived in all situations other than eunuchoidism (probably lasting no longer than one to two months). The decrease in nitrogen excretion can be accounted for by a decreased urea formation. Estrogens are much weaker anabolic agents than are androgens and probably do not exert at physiological levels an anabolic action on non-sexual tissue.

THE FATE OF THE RETAINED NITROGEN

14. Kochakian, C. D. Symposium on Steroid Hormones. University of Wisconsin Press, 1950, p113.

15. Scow, R. O., and S. N. Hagan. Effect of testosterone propionate on myosin, collagen, and other protein fractions in striated muscle of gonadectomized rats. Endocrinology 60:273, 1957.

16. Scow, R. O., and S. N. Hagan. Effect of testosterone propionate on myosin, collagen, and other protein fractions in striated muscles of gonadectomized male guinea pigs. Am. J. Physiol. 180:31, 1955.

17. Scow, R. O. Effect of testosterone on muscle and other tissues and on carcass composition in hypophysectomized, thyroidectomized, and gonadectomized male rats. Endocrinology 51:42, 1952.

18. Kochakian, C. D. Mechanisms of androgen actions. Laboratory Investigation 8:538, 1959.

19. Szirmai, J. A. Histological aspects of the action of androgens and oestrogens, ch. in Protein Metabolism, Berlin: Springer-Verlag, 1962, p45.

Of the increase in body weight (14%) in gonadectomized rats given testosterone, 25% of the weight gain (and possibly a larger percentage of the retained nitrogen) occurs in the accessory sex tissue. Testosterone has no appreciable effect on the weight of thigh muscle, heart, liver, and bone or on the percentage of carcass protein. Furthermore, only a small number of striated muscles (such as the levator ani muscle of the rat, the temporalis muscle of the guinea pig, and the pectoral muscles of the bull) are testosterone-sensitive. In the normal male rat given testosterone the only increase in weight, according to Kochakian, is probably due to an increased food intake. Histologically, the response can be shown to be an increase in the diameter of muscle fibers and fibrils.

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The most careful anthropometric and histological studies of sexual differences in musculature in humans. These studies suggest that the pectoral and shoulder muscles are the

most responsive muscles to testosterone in man. Most muscles probably show a graded responsiveness; in general, in most animals and probably in man, the most sensitive skeletal muscles to testosterone are those which support the limbs and particularly the forelimbs.

DISSOCIATION OF ANDROGENIC AND ANABOLIC ACTIONS

22. Drill, V. A., and B. Riegel. Structural and hormonal activity of some new steroids. Recent Progress in Hormone Research 14:29, 1958.

23. Desaulles, P. A., and C. Krahenbuhl. Evaluation and mode of action of anabolic steroids: differentiation of action of various anabolic steroids, ch. in Protein Metabolism, Berlin: Springer-Verlag, 1962, p170.

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26. Tepperman, J. Metabolic and Endocrine Physiology. Chicago: Yearbook Medical Publishers, 1962, p56.

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Also, see ref. 13.

These papers review the pharmacologic techniques by which anabolic functions of steroid hormones are defined; the difference in weight between the seminal vesicles of treated and untreated rats gives a measure of androgenic activity whilst the difference in weight of the levator ani muscle gives a measure of the myotrophic (anabolic) activity of the steroids. In the usual testing procedure, a given hormone is compared with a reference hormone (usually testosterone). The weaknesses of such testing have been pointed out by Tepperman and by Dorfman and Shipley. Desaulles convincingly argues that these do not represent different actions of the same hormone but only represent different affinities, concentration, degradation, etc. of specific hormones by specific tissues. No purely anabolic hormone without androgenic effects has ever been found.

28. Wilkins, L., and W. Fleischmann. The influence of various androgenic steroids on nitrogen balance and growth. J. Clin. Endocrinol. 6:383, 1946.

29. Henderson, E., and M. Weinberg. Methylandrostenediol. J. Clin. Endocrinol. 11: 641, 1951.

30. Partridge, J. W., L. Boling, L. de Wind, S. Marger, and L. Kinsell. Metabolic and clinical effects of methylandrostenediol in human subjects. J. Clin. Endocrinol. 13:189, 1953.

31. Kosdon, S. C., W. H. Fishman, R. M. Dort, C. D. Bonner, and F. Hamburger. Methylandrostenediol in palliative treatment of breast cancer. JAMA 148:1212, 1952.

These papers are representative of most careful human studies with the older "anabolic" steroids. In general, most anabolic agents so far tested in man have a weaker and less sustained effect on nitrogen metabolism than does testosterone. Androgenic side effects

nearly always occur at levels which cause a significant effect on nitrogen balance. In instances in which positive nitrogen balance is not the therapeutic aim such as breast cancer (Ref. 31) it may be possible to give larger doses with less virilization, and, in fact, a greater survival rate has been claimed for the weakly anabolic steroid methylandrosterediol than for testosterone in this condition.

32. Nowakowski, H. Metabolic studies with anabolic steroids. Acta Endocrinologica Supp. 63, p37, 1962.

33. van Wayjen, R. G. A., and G. Buyze. Clinical-pharmacological evaluation of certain anabolic steroids. ACTA Endocrinologica Supp. 63, p18, 1962.

In doses of 50-100 mg. every 14-24 days Nandrolone was able to induce a positive nitrogen balance in 14 patients, even in the face of a prednisolone induced negative nitrogen balance. Unfortunately, these are very short term studies.

34. Liddle, G. W., and H. A. Burke, Jr. Anabolic steroids in clinical medicine. Helvetica Medica ACTA 27:504, 1960.

The only published paper in which the actions of three anabolic steroids (Nandrolone, fluoxymesterone, and Δ^1-methyltestosterone) have been compared in man with methyltestosterone. In these studies Δ^1-methyltestosterone had by far the most potent effect on nitrogen metabolism (10 X that of an equal weight of methyltestosterone). Furthermore, maximal effects on nitrogen balance can be produced by doses (1.25-2.5 mg. per day in adults) which almost never produce virilism, acne, or BSP retention. It appears that at the present time Δ^1-methyltestosterone is the only anabolic steroid in which in humans, the anabolic and androgenic effects can be differentiated in most cases. It is very important to recognize, however, that this hormone has not been shown to be myotrophic in humans, that the fate of the retained nitrogen is unknown, and that its effect is probably short lived.

CLINICAL USEFULNESS OF ANABOLIC STEROIDS

1. Undernutrition and Debilitation

35. Leathem, J. H. The influence of nutrition and nutritional status on the effect of androgens and anabolic agents, ch. in Protein Metabolism, Berlin: Springer-Verlag, 1962, p202.

In the repletion of rats after starvation, anabolic steroids have virtually no additional effect above that of refeeding alone, e.g. when protein synthesis is maximal it cannot be further accelerated by anabolic agents.

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37. Forsyth, B. T. The effect of testosterone propionate at various protein and caloric intakes in malnutrition after trauma. J. Lab. Clin. Med. 43:732, 1954.

38. Howard, J. E., J. Winternitz, W. Parson, R. S. Bigham, and H. Eisenberg. Studies on fracture convalescence. Bull. Johns Hopkins Hosp. 75:209, 1944.

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In humans recovering from severe trauma or surgery, testosterone administration can usually produce a further increase in positive nitrogen balance. This slight gain has not been demonstrated to be of therapeutic benefit.

41. Watson, R. N., M. H. Bradley, R. Callahan, B. J. Peters, and R. C. Kory. A six month evaluation of an anabolic drug, norethandrolone, in underweight persons. Am. J. Med. 26:238, 1959.

42. Kalliomaki, J. L , A. M. Pirila, and I. Ruikka. A therapeutic trial with ethylestrenol in geriatric patients. ACTA Endrocrinologica Supp. 63, 1962, p124.

43. Simonson, E., W. M. Kearns, and N. Enzer. Effect of methyl testosterone treatment on muscular performance and central nervous system of older men. J. Clin. Endocrinol. 4:528, 1944.

44. Vernon, P. E., and M. McKinlay. Effects of vitamin and hormone treatment on senile patients. J. Neurol. 9:87, 1946.

Any effect of anabolic steroids on weight in undernourished or debilitated individuals is probably due to enhanced appetite. In double blind studies of elderly individuals no effects on weight, strength, or psychological tests have been documented following anabolic steroid therapy.

II. Osteoporosis

45. Kowalewski, K. Effects of steroids on bone formation, ch. in Protein Metabolism, Berlin: Springer-Verlag, 1962, p238.

This paper reviews the relationship between anabolic steroids and the metabolism of the connective tissue of bone. Anabolic steroids (particularly Δ^1-methyltestosterone) can clearly prevent cortisone induced osteoporosis in rats and chickens.

46. Reifenstein, E. C., and F. Albright. The metabolic effects of steroid hormones in osteoporosis. J. Clin. Invest. 26:24, 1947.

47. Albright, F., and E. C. Reifenstein. The Parathyroid Glands and Metabolic Bone Disease, Baltimore: The Williams & Wilkins Co., 1948, p145.

48. Schoene, R. H. A clinical approach to senile osteoporosis. Ohio State Medical Jour. 48:126, 1952.

49. Bartter, F. C. Osteoporosis. Am. J. Med. 22:797, 1957.

50. Reifenstein, E. C. The rationale for the use of anabolic steroids in controlling the adverse effects of corticoid hormones upon protein and osseous tissues. South. Med. Jour. 49:933, 1956.

51. Henneman, P. H., and S. Wallach. A review of the prolonged use of estrogens and androgens in postmenopausal and senile osteoporosis. Arch. Int. Med. 100:715, 1957.

52. Dymling, J. F., B. Isaksson, and B. Sjogren. Anabolic steroids in the treatment of osteopenia. Protein Metabolism, Berlin: Springer-Verlag, 1962, p412.

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Both estrogens and androgens produce a positive calcium balance; only androgens have a consistent effect on N balance. Estrogen and androgen combined have a greater effect on Ca balance than either alone. However, in Henneman's 20 year followup of over 200 of Albright's patients not one had evidence of recalcification. Even so, impressive evidence was obtained that the progression of the disease was stopped, and pain was well controlled (47, 48, 51). The discrepancy between short term balance studies and long term treatment suggests that there is a limit to the amount of bone formation which can be induced by steroids in man. The only reversible form of osteoporosis in man is in Cushings disease. In addition Reifenstein has pointed out that anabolic steroids can prevent the osteoporosis which ensues in long term corticoid therapy.

III. Renal Failure

54. Thaysen, J. H. Anabolic steroids in the treatment of renal failure, ch. in Protein Metabolism, Berlin: Springer-Verlag, 1962, p450.

55. Blagg, C. R., and F. M. Parsons. The use of norethandrolone in acute renal failure from obstetric causes. Lancet II, 1960, p577.

56. Gjorup, S., and J. H. Thaysen. The effect of anabolic steroid (durabolin) in the conservative management of acute renal failure. Acta Medica Scandinavica 167:227, 1960.

57. Parsons, F. M. Norethandrolone in acute renal failure. Lancet I, p148, 1959.

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59. Blagg, C. R., F. M. Parsons, and G. A. Young. Effect of dietary glucose and protein in acute renal failure. Lancet I, 1962, p608.

60. Gjorup, S., and J. H. Thaysen. Anabolic steroids in treatment of uremia. Lancet II, 1958, p886.

Anabolic steroids are of no practical value in chronic renal failure; they can produce a transient positive nitrogen balance without worsening of the renal failure, but this is of doubtful significance. In acute renal failure, 29% of patients (those who had a low rate of catabolism before treatment) had a fall in the rate of urea production (averaging about 60%) and consequently lowering the frequency of dialysis. This effect seems to be most consistent in post partum cases. In view of the fact that only the non-hypercatabolic patients respond and these do well anyway, the use of anabolic agents in acute renal failure is probably of little value.

IV. Hematologic Disorders

61. Finkelstein, G., A. S. Gordon, and H. A. Charipper. The effect of sex hormones on the anemia induced by hemorrhage in the rat. Endocrinology 35:267, 1944.

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63. DeBias, D. A. Effect of testosterone propionate on red cell count in ovariectomized and ovariectomized thyroidectomized rat. Am. J. Physiol. 165:476, 1951.

64. Aschkenasy, A., and F. Dray. Action de la thyroxine, des hormones corticotrope et somatotope et des hormones genitales sur la regeneration sanguine apres inanition proteique. Surg. 25:461, 1954.

Testosterone accelerates the recovery from the anemia of undernutrition and of hemorrhage in the rat. Splenectomy in the hamster prevents this response to testosterone, and thyroidectomy in the rat prevents the increase in the peripheral RBC but not the repair of the bone marrow.

65. Hamilton, J. B. The role of testicular secretions as indicated by the effects of castration in man and by studies of pathological conditions and the short lifespan associated with maleness. Rev. Prog. Hormone Res. 3:280, 1948.

Within 20 days after castration in man maximal changes have occurred - a 10% fall in RBC, a 36% decrease in cell diameter, a marked increase in osmotic fragility. There is an increase of sedimentation rate of 174% following castration in the male. In occasional castrates the anemia may be quite severe.

66. Kennedy, B. J., and A. S. Gilbertson. Increased erythropoiesis induced by androgenic-hormone therapy. NEJM 256:719, 1957.

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Thirty-five percent of women treated with pharmacological doses of testosterone (300 mg/week) for carcinoma of the breast had a marked hematologic response, irregardless of the previous level of hemoglobin or the progression of the carcinoma. The maximal hematological response occurred in 2-11 mos., was invariably preceded by flushing and a plethoric appearance. The average hemoglobin rise was 4.3 gms.% and hematocrit rise was 11%. Bone marrow revealed a normoblastic hyperplasia. In one woman the hemoglobin rose as high as 21 gm% (from a previous low of 6).

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The higher hemoglobin concentration in males (2 gm%) is hormonal in origin. There is no sex difference in the number of leucocytes or platelets. Furthermore, children with adrenogenital syndrome have a high hemoglobin (which falls to normal following replacement therapy with hydrocortisone). The suggestion has been made that polycythemia occurs only in those cases of Cushings Disease with high androgen secretion.

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72. Gardner, F. H., and D. G Nathan. Hypochromic anemia and hemachromatosis. Response to combined testosterone, pyridoxine, and liver extract therapy. Am. J. Med. Sciences 243:447, 1962.

73. Shahidi, N. T., and L. K. Diamond. Testosterone induced remission in aplastic anemia. J. Dis. Child. 98:293, 1959.

74. Shahidi, N. T., and L. K. Diamond. Testosterone induced remission in aplastic anemia of both acquired and congenital types. NEJM 264:953, 1961.

75. Bouroncle, B. A., and C. H. Doan. Myelofibrosis: Clinical, hematologic, and pathologic study of 116 patients. Am. J. Med. Sciences 243:697, 1962.

76. Lehnhoff, H. J. Androgen therapy for refractory anemia: report of a case associated with thymoma. Ann. Int. Med. 53:1059, 1962.

77. Rucknagel, D. L., and A. L. Chernoff. Immunologic studies of hemoglobins. III. Fetal hemoglobin changes in the circulation of pregnant women. Blood 10:1092, 1955.

These reports document the non-specific nature of the erythroid response to testosterone therapy in that a whole variety of anemias may respond - hypoplastic anemias, the anemia of myeloid metaplasia, the anemia of myeloma, lymphoma, etc. In patients with myeloid metaplasia, those patients who respond frequently had worsening of the hyperuricemia and splenomegaly. Gardner and Nathans (72) argued on the basis of a single, very well studied case that this action of testosterone is due to an enhancement of the differentiation of stem cells into erythroblasts and of erythroblasts into mature RBC.

THE SIDE EFFECTS OF ANABOLIC STEROID THERAPY

78. Kory, R. C., M. H. Bradley, R. N. Watson, R. Callahan, and B. J. Peters. A six-month evaluation of an anabolic drug, norethandrolone, in underweight persons. II. BSP retention and liver function. Am. J. Med. 26:243, 1959.

79. Arias, I. M. The effects of anabolic steroids on liver function, ch. in Protein Metabolism, Berlin: Springer-Verlag, 1962, p434.

80. Foss, G. L., and S. L. Simpson. Oral methyltestosterone and jaundice. British Med. J. I, 259, 1959.

All 17-α substituted anabolic steroids studied so far regularly produce BSP retention and frequently conjugated hyperbilirubinemia (bilirubin diglucuronide formation is normal). Evidence suggests that the level of interference is at the site of transport of metabolites from the liver cell into bile. The incidence of clinical manifestations of this abnormality of liver function probably depends upon the previous integrity of the liver. When BSP retention exceeds 40% jaundice almost invariably results.

81. Federman, D. D., J. Robbins, and J. E. Rall. Effects of methyl testosterone on thyroid function, thyroxine metabolism, and thyroxine-binding protein. J. Clin. Invest. 37:1024, 1958.

This drug (as do all anabolic steroids) produces a striking fall in thyroxine binding protein in blood and a slight fall in PBI.

82. Muller, A. F., M. Valatlan, and E. L. Manning. Effet de la 17-ethyl-19-nortestosterone sur la secretion du cortisol. Helvetica Medica Acta 27:678, 1960.

Nilevar inhibits the conjugation of adrenal corticoids in the liver, as a result of which the secretory rate falls, and the excretion of 17-OH and 17-keto steroids falls. FSH secretion also falls to zero.

83. Huggins, C. Endocrine substances in the treatment of cancers. JAMA 141:750, 1949.

Although there is no evidence that androgen therapy induces malignancy, it does tend to promote growth and intensify pain in both carcinoma of the prostate and carcinoma of the male breast.

84. McCullagh, E. P., and H. R. Rossmiller. Methyl testosterone. I. Androgenic effects and the production of gynecomastia and oligospermia. J. Clin. Endocrinol. 1:496, 1941.

Gynecomastia is a relative infrequent occurrence except at high doses, but in 70-80% of men given 75 mg. testosterone per week or 75-200 mg. methyltestosterone per day, oligospermia results. It occurs within a few weeks after therapy begins, and the count rises again after it is stopped.

85. Laron, Zui. Effectiveness of fluoxymesterone on linear growth and weight in children with growth retardation and underweight. ACTA Endocrinologica 36:541, 1961; also in Protein Metabolism, Berlin: Springer-Verlag, 1962, p398.

Most children who receive fluoxymesterone or Δ^1-methyltestosterone have an increase in urinary estrogen (two to 10 fold), probably explaining the gynecomastia.

86. Kearns, W. M. Oral therapy of testicular deficiency. J. Clin. Endocrinol. 1:126, 1941.

The occasional edema which results is usually encountered only in those individuals receiving large doses (75 mg/week testosterone). The tendency to form edema may be greater in cardiacs. This side effect has also been noted in the cancer chemotherapy studies (Ref. 67).

The clinical aspects of virilism in women receiving enormous doses of anabolic agents has been reviewed by Kennedy and Nathans (67), and the virilizing side effects of the more potent anabolic agent, Δ^1-methyltestosterone, has been reviewed by Liddle (34), who points out that children may develop virilizing signs on minute doses of these drugs.

87. Berczeller, P. H., and H. S. Kupperman. The anabolic steroids. Clin. Pharm. & Therapeutics 1:464, 1960.

88. Fruehan, H. E., and T. H. Frawley. Current use of anabolic steroids. JAMA 184: 527, 1963.

These papers review not only the side effects and are also good reviews of the therapeutic use of these agents.