

1953

Steroid hormone in geriatrics

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THE STEROID HORMONES IN GERIATRICS

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

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May 15, 1953

Omaha, Nebraska

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STEROID HORMONES IN GERIATRICS

The male and female gonadal hormones and the hormones of the adrenal cortex are related to the cholane and sterol series of organic substances by containing the hydrogenated cyclopentenylphenanthrene (Steroid) nucleus, as described in Whitmore's Organic Chemistry (1). Diethylstilbestrol, the widely used synthetic estrogenic substance, is not a member of this chemical group. See Fig. 1.

Study of the physiologic effect with relation to structure is not complete, but Scope (2), summarizing this work, states that the side chain at C17 and ketone at 3 are necessary to adrenal cortical activity, those hormones with only those groupings being inorganic metabolism regulators. Properties regulating organic metabolism are added by a hydroxy or ketone group at C11 and intensified by these groups if also on C17. The hydroxy or ketone groups at C17 depress inorganic metabolism. See Fig. 2.

The process of aging has quite naturally been associated with the decline of sexual powers, which Turner (5) describes as the most resented aspect of aging. Pepper (6) points out the many schemes developed over the years to preserve or repossess sexual potency. According to Kirk, Brown-Sequard (7), by using a testicular extract on himself, pioneered the clinical use of testosterone. The book by Biedl (8) published in 1913 compiled

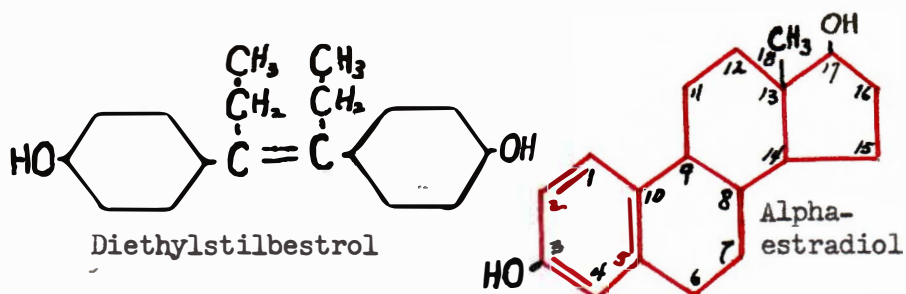


Fig. I Comparison of diethylstilbestrol and a natural estrogen with the steroid nucleus in red. Ref. Griboff (3)

Common Name	Chemical Name	Chemical Configuration			
DOC	11-Desoxy-corticosterone				
Compound A	11-Dehydro-corticosterone				
Compound B	Corticosterone				
Compound E (Cortisone)	17-Hydroxy 11-dehydro- corticosterone				
Compound F (Hydrocortisone)	17-Hydroxy- corticosterone				
Androgen	Testosterone				
Androgen	Androsterone				
Androgen	11-Hydroxyiso- androsterone				
Androgen	17(a)-Hydroxy- progesterone				
Estrogen	Progesterone				
Estrogen	Estrone				

Fig. II Other common steroids and their characteristic features. Ref. Anonymous (2&4) and Griboff (3)

the literature on endocrinology of that time, and included many basic assay and isolation methods for the adrenal cortical and the sex hormones.

Upon these foundations medicine continues to build, the progress having been greatly accelerated by the availability of many specific substances which lend themselves to well-controlled clinical testing. There is promise that desirable effects can be separated from untoward reactions of the natural substances. Holland (9) points out two of these substances. Chlorotrianisene, a synthetic estrogen, which when used in patients who had a severe gastric irritation from diethylstilbestrol was well-tolerated. Methylandrostenediol is a non-virilizing steroid with moderate protein anabolic effect, producing objective and subjective response in late metastatic breast cancer without water retention and hypercalcemia.

The boundaries of geriatric medicine are very indefinite, their extent depending upon the person who is defining the term. While Clow (10) limits this to treatment of those in the "declining years" and places the arbitrary age minimum at sixty years, according to Stiedlitz (11) it deals with the physiologic and pathologic problems of older individuals, then he hastens to explain that aging begins with conception and ends at death. Further, he differentiates chronologic age and biologic age, which are rarely

the same, and emphasizes that no organism is of uniform physiologic age throughout. He more specifically defines the limits of gerontotherapy in the following outline (Fig. 3) of diseases of later maturity (12).

The fountain of youth has always been an extremely attractive but elusive treasure. Many researchers since Brown-Sequard have looked to the steroid hormones as possible therapeutic agents to be used in the reversal or, perhaps, at least, to slow the creeping degeneration of aging individuals. There is evidence in certain experiments that a return to a more youthful condition of certain organs can be produced.

The target organs of estrogen were studied histologically by Masters (13) in a group of senile women before, during, and after a course of estrogen-progesterone therapy. He produced cyclic bleeding "similar to normal menstruation" with his program, and found both gross and microscopic evidence of rejuvenation in the vaginal mucosa, uterus and breast. In the uterus and ovary there was especially increased circulation with recanalization of arteries. The ovarian tissue, however, showed no response.

Kirk (14-15) showed that there was a decline in the acid phosphatase activity of prostatic secretions in old men, and then treated some of them having especially low values with testosterone for periods up to six months. He found little if

CHRONIC PROGRESSIVE DISORDERS
OF LATER MATURITY

- A. Circulatory Disorders
 - 1. Chronic Infective
 - a. Rheumatic
 - b. Luetic
 - 2. Hypertensive Arterial Disease
 - 3. Arteriosclerosis
 - a. Cerebral
 - (1) Apoplexy
 - (2) Dementia
 - (3) Encephalopathy
 - b. Coronary
 - c. Renal--Chronic Nephritis
 - d. Pancreatic Gangrene
 - e. Buerger's Disease
 - 4. Combination forms
- B. Metabolic Disorders
 - 1. Diabetes Mellitus
 - 2. Anemia
 - 3. Climacteric (Male and Female)
 - 4. Gout
- C. Malignant Tumors, all forms
- D. Arthridides

Figure 3. Outline of Geriatric Conditions, Ref. Stiedlitz, (12).

any improvement in the acid phosphatase levels during the treatment, and concluded that the prostate of these individuals was unable to respond to a stimulus which would produce response in younger men.

The non-target organs have also been studied during the administration of the sex steroids, both locally and systemically. Changes in the skin were studied after local application of steroids by Goldzieher et.al. (16). He described proliferation of the epidermis with development of the rete pegs and papillae, increased production of keratohyalin granules, new formation of elastic fibrils, and increased vascularization of the cutis. These changes were noted to be more prominent when estrogen was the agent used. The changes are a result of a property of the steroid other than its sexual potency, for both the androgenically weak 17-methylandrostenediol and estrogenically inactive beta-estradiol produced the skin changes.

Similarly, the nasal mucosa of elderly individuals was noted by Votow (17) to show changes which he considered should be of value in the management of nasal problems.

Friedlander and Perlman (18) studied the effect of some steroids on the human heart. Pregnenolone has been shown to depress contractility but increase the rhythmicity of the heart. Progesterone decreased the threshold of excitability and produced

spontaneous extrasystoles.

A new study reported by Pick et al. (19) which, while done on cholesterol-fed cockerels, will no doubt stimulate further study of interest to gerontologists. In this study the atherosclerosis of the coronary vessels usually found in chicks fed such a diet was almost completely eliminated by the administration of estrogen throughout the test period. It was noted by chemical study of the blood that any failure was predictable by the cholesterol-lipid phosphorus ratio which was above 20 in these cases. All chicks in which coronary atherosclerosis did not develop had a C/P ratio less than 20. Another interesting observation was that aortic atherosclerosis developed in all chicks of the cholesterol diet, indicating that the atherogenesis did not proceed according to the same biologic laws in the two vascular beds.

The protein anabolic effect of sex steroid administration to aged individuals produces very desirable gains in weight, increase in muscle mass and tone, and increased vigor. Kenyon et al. (20) and Kountz (21) have made metabolic studies which show that while both estrogen and androgen are effective, the androgen produces the greater change. Kountz states that most old people were found to be in negative nitrogen balance unless their intake of protein was greater than one gram per kilogram of

body weight. During sex hormone therapy however, both studies showed that there was a shift to positive nitrogen balance without increasing serum nitrogen, indicating utilization was accomplished. There may be a gain of eight or more pounds in four to eight weeks in subjects over 70 and an increase in muscular strength is also noted. Calcium is also retained, but there may or may not be X-ray evidence of remineralization of bone. For this reason it is considered by Albright (22) that the sex steroid action is that of increased matrix formation due to general anabolic activity rather than specific bone formation properties.

Caldwell and Watson (23) made observations on the psychologic response to long term sex steroid administration in women. The study was done by giving a battery of intelligence and psychometric examinations before starting therapy, and then repeating the tests in six months, and again at one year after the start of hormone replacement. It was their conclusion that most patients improved in thought and memory while others merely did not decline. While they showed no decline among treated patients there were three of eight patients in the control group who improved 0.05 level, while five declined. In the treated group eleven of seventeen patients improved 0.05 level. The series is small and it would seem that improvement in nearly

half of the control group would be reason to question whether or not similar improvement in the treated patients could be taken as a criterion for judging success of the medication in producing the change. Others have, however, expressed the opinion that apparently there is improvement in mental activity, the appearance of an optimistic outlook, and a general feeling of well-being in older people treated by sex hormones for whatever reason. Goldzieher and Goldzieher (24) report that the creative output of an "aged artist" varied both qualitatively and quantitatively directly with his physical response to various doses and courses of steroids over a period of six and one-half years.

Opinion about the advisability of using the sex steroids in attempts at rejuvenation and reversal of senile changes varies, but in general there are words of caution. Kirk (15) feels since his work with testosterone and the prostatic secretions that, as he found in the case of this primary target organ, other organs may have lost their ability to respond to the sex hormones. He says that to his knowledge such treatment has not prolonged life, and it may theoretically shorten it, since even such desirable effects as sense of well-being, increased muscle power, etc. may be responsible for an increase in activity which the cardiovascular or other unresponding system may be incapable of supporting. Cordonnier(25) condemns the use of testosterone

without specific indication, since a study he made of twenty-three elderly male patients receiving this hormone over a "long period" revealed histologic evidence of testicular atrophy in eleven. Kornechevsky (26, 27, 28) in his work on both rats and human subjects presents evidence to indicate that senility and the castration syndrome are not equivalents, and that treatment with the sex steroids produces different results when used in intact subjects than that produced when used in the castrate. He concludes that senile degeneration of the gonads is but one effect of senility rather than a primary etiologic factor, and that while reversal of some of the senile changes may be produced by hormone administration such dosage also is capable of producing pathological changes and even change in the nature of the organism.

Benjamin (29) on the other hand, after using various combinations of steroid hormones given together according to the symptomatology, concluded that this was a most promising approach to gerontotherapy.

Solez (30) has compiled a great mass of evidence from the literature to point out the similarity between Cushing's syndrome and aging. This section reviews his work in part and incorporates some new literature.

Farber (31) et al, noted that children with Cushing's syndrome appeared prematurely old, and further, the fact that

although there was in them an early maturation of sexual function, there followed rapidly a decline in these functions. If, as mentioned before, the gonadal degeneration is not primary in senility and there is some similarity between a significant number of the symptoms of senility and a disease known to be a result of increased adrenal cortical activity in younger individuals one then suspects that there may be an etiologic roll of the adrenal in aging.

Many of the diseases that not only have an increased incidence in older people but also have been considered to be a result of the aging process itself have been related to adrenal pathology.

Anderson (32) concludes that the preponderance of evidence points to the adrenal as being an important factor in hypertension. Rather (33) demonstrated adrenal hypertrophy following the experimental production of a renal hypertension in laboratory animals by restricting one kidney and removing the other. Both medulla and cortex of the adrenal increased in size, the cortex becoming two to three times normal while the medulla became five times normal. Commons (34) testing hormonal changes with age found that the androgen level decreased while there was no decrease in desoxycorticosterone or 11-hydroxy-17-hydroxycorticosterone and suggested that in order to maintain normal

hormonal balance, supplementary androgen might be desirable. Friedman (35) produced a permanent hypertension by administration of desoxycorticosterone acetate to laboratory animals. He found that he could relieve this hypertension by injection of lipo-adrenal-cortex (a strong adrenal cortical extract).

Solez (30) believes that the increased facial hair growth seen in postmenopausal women is suggestive of the predominance of the adrenal cortical hormone at that time. This may be either relative, due to loss of gonadal hormone, or absolute, in which case the increase in adrenal activity could be a result of general hyperactivity of the anterior pituitary as indicated by high levels of gonadotropic hormone. The male analog of this condition is the increase of hair growth in the nose and external ears.

It is well known that diabetes mellitus incidence increases with age and also that diabetes and hypertension are frequently associated in this age group. This could, of course, be that both are diseases of older people and thus only incidentally associated. The fact that both are seen together in Cushing's syndrome and also that Russi et al. (36) describes an increased incidence of adrenal cortical adenomas associated with both conditions suggests a common etiologic factor, perhaps adrenal dysfunction.

After a study of the urinary excretion of steroids in women before, during and after the menopause, McGavack (37) concludes that the adrenal was directly connected to the etiology of aging. When diseases of aging appeared in these patients after the menopause, the cases were reclassified according to the predominant complaint. In the first group, those with hypertrophic arthritis which was frequently associated with hypertensive cardiovascular disease at the menopause, 77% had an abnormal response to DCA and salt (considered as evidence of increased production of mineral corticoids), with 50% showing low BMR and 25% showing low 17-ketosteroid, but no significant change in 11-oxycorticoid. The second group, those with hypertensive cardiovascular disease appearing after menopause which was frequently associated with hypertrophic arthritis, there was abnormal response to DCA and salt in eight of ten patients, with no significant change in BMR, 17-ketosteroid or 11-oxycorticoid levels. The third group, in which he considered the evidence equivocal, the patients developed diabetes mellitus, Acard-Thiers syndrome, or osteoporosis, and showed only 61% increase in 11-oxycorticoids (glucocorticoids) and this was associated with altered 17-ketosteroid in 50%.

Therapy directed toward the adrenal in aged individuals has not been extensively studied. Albright (38) working on the treatment of Cushing's syndrome postulated that the disease was the

result of the predominance of S. hormone (protein antianabolic) and thus treated it by injection of N hormone (protein anabolic) and had excellent results. The patients were not only benefited clinically, but chemical studies revealed a tendency toward protein rebuilding and bone matrix formation. Thorn(39) states that there is evidence that the rice diet, long used in hypertensive states, actually does decrease adrenal cortical activity. He also feels that the use of adrenalectomy, which has been used in a limited way for hypertension, will become more useful in the future with the use of corticosterone (compound B) as the replacement substance. Corticosterone not only has a wide latitude of safety but has both organic and inorganic metabolic effects.

One of the earliest manifestations of physiologic degeneration is the cessation of the menses in women, and it is often accompanied by a variety of symptoms, some of which are quite generally disabling. Although the factors of declining ovarian activity, susceptibility of the autonomic nervous system, and emotional stability of the individual all have been shown by Greenblatt (40) to play a part in the symptomatology of the menopause, the decline in ovarian activity seems to be the key factor. Since abrupt cessation of the ovarian activity such as in surgical menopause, is usually followed by severe symptomatology, it is postulated that the severity depends upon the speed of ovarian

decline. This theory is further supported by the fact that Brown et al. (41) implanting estradiol pellets simultaneously with the removal of ovaries report success in avoiding the usual severe menopausal symptomatology usually seen in such cases.

Much has been stated about the increased pituitary activity as reflected in increased FSH levels found in urine of these patients. Since, however, the FSH titers remain high for years after symptoms of the menopause disappear, Greenblatt (40) feels that they are a result of estrogen decline but are not responsible for the symptoms.

Steroids are used to alleviate the complaints of the patient who is experiencing the menopausal syndrome difficulties. The treatment depends upon the predominant complaint, which may be any one of several, all a part of the menopausal syndrome.

Postmenopausal bleeding, according to Greenblatt (42), can be brought under control quickly and easily by the use of estrogen. He prefers, however, to use a combination of steroids, consisting of estradiol benzoate 1.66 mg., progesterone 25 mg., and testosterone propionate 25mg. daily for five days. This treatment, done only after endometrial and cervical carcinoma are ruled out, is said to decrease bleeding within 24 hours, then a withdrawal episode lasting five to six days after the course of steroids is discontinued.

Urinary frequency and nocturia, on the other hand, is said to be treated best by the use of androgens alone. Greenblatt (43) states that even though estrogen will also alleviate the symptoms, there is the possibility that postmenopausal women may also have unrecognized breast or genital cancers, and it is advisable whenever one can do so to use androgen therapy.

Whether X-ray evidence of arthritis is present or not, painful, stiff, and sometimes swollen joints are seen following the menopause. That this is a true menopausal arthralgia is shown by Greenblatt (40) who has observed it associated with artificial menopause as well. He has treated the condition with estrogen and after a period of relief substituted cortisone. The symptoms returned on this drug, but were again relieved by reinstating estrogen therapy.

According to Hart (44) menopausal osteoporosis may manifest itself only by backache and/or pelvic pain without sufficient decalcification for making a conclusive radiological diagnosis. Administration of estrogen and androgen or either drug alone will relieve the symptoms. Postmenopausal osteoporosis which occurs years after the cessation of the menses shows considerable decalcification by X-ray. Albright (22) uses high protein diet, estrogens and androgens with gradually increased exercise as tolerated. The relief of pain

may be the only indication of improvement as a ctual X-ray studies may not show any increased calcification.

In Greenblatt's (40) experience menopausal headache is not usually benefited by estrogen. The use of androgen or a combination of estrogen and androgen, however, has produced relief of very severe and incapacitating headaches that in some cases have been mistaken for migraine.

Greenblatt (40) points out that the hormones are used in the menopause only in those women who show severe symptoms. For the others he uses reassurance, and if necessary, autonomic depressant drugs and mild sedation. When hormones are indicated, the regime of therapy is initiated by injection of estradiol benzoate 1x66 mg. once daily or every other day depending on symptoms. Then a gradually decreasing oral dose schedule is substituted, beginning with estrogen sulfate 3.75 mg., 0.15 mg. ethinyl estradiol or 0.3 mg. stilbestrol per day divided into three doses. After one month the daily dose is reduced by giving the single dose amount twice daily, then in one month once daily. The treatment is extended to five or six months by reducing to one-half the individual dose daily and then the same amount every otherd ay. As recommended in connection with each special manifesta- tion of this syndrome, androgen or estrogen and androgen together may be preferable, but in general the authors all agree that a

planned gradual reduction and stopping the therapy is necessary. Geist and Solomon (45) and Benjamin (29) state that in the female they recommend using combined estrogen and androgen therapy or androgen therapy alone, in any case to avoid complications of estrogen therapy, especially uterine bleeding and the possibility of aggravating a neoplasm.

DeCourcy (46) sees cancer as a rejuvenation attempt in tissue which comes about after degeneration, whether that be early due to specific conditions, or later due to "normal" processes, but which would take place in all tissue if it lived long enough. He states that the degenerative changes of the precancerous state cannot be distinguished from those of normal senescence. For every degeneration there must be a cause, and where there is a cause a means of prevention or counteraction may be sought. Whatever the cause, malignant neoplasms are more prominent in the later years.

Since Beatson (47) in 1896 directed attention to the ovary as a possible etiologic factor in the cause of carcinoma of the breast, the steroid hormones have been both condemned for causing and praised for their therapeutic action in various cancers. It was in 1900 that Boyd (48) reported on therapy of mammary carcinoma by oophorectomy. All of this occurred long before Lacassagne (49) in 1932 showed that such cause and effect relationship existed between estrogen and breast cancer of animals. There

is no proof positive that this is the case in humans; most authors agree, however, that the estrogens tend to aggravate growth. In therapy there is a paradox, since according to Nathanson (50) in certain premenopausal women estrogen dosage sufficient to cause amenorrhea will benefit the patient with mammary carcinoma, and it is universally agreed that in postmenopausal patients the effectiveness of ordinary doses of estrogen become increasingly effective with the number of years since the menses ceased.

Haddow (51) discovered the effect of estrogens while working with carcinogenic hydrocarbons with weak estrogenic activity by noting that they retarded the growth of malignant tissues. The first report of the use of androgens in breast cancer was made by Loesser (52).

Since Beatson, volumes have been written on the steroids and breast cancer, yet the fact remains that surgery is the only cure, and therefore the first treatment in any case which appears within the reach of the knife. Radiation of metastatic lesions has its place, but according to Hines (53) there is a tendency for irradiated tumors to respond poorly to hormone therapy and also, conversely, that tumors treated by hormone therapy tolerate radiation poorly.

Androgen therapy has been widely studied. The improvement is usually dramatic with reports by Adair (54), Adair and

Herrmann (55) Adair et al. (56) citing instances of bedridden patients with extensive metastases soon sleeping without sedation and in several months returning to their household duties. This response cannot be taken entirely as evidence of arrest and regression of the tumor, however, for it has been observed by the Council on Pharmacy and Chemistry (58, 59, 60), DeCourcy (61), Preston, et al. (62), Prudente (63), Taylor et al. (64), that symptomatic relief is shown even in cases in which the metastatic lesions continue to progress. The subjective responses most frequently reported were relief of pain of osseous metastases, increased appetite, strength, and weight, and a sense of well-being. In those patients showing objective response the metastatic lesions of bone are more favorably affected, and affected earlier in the course of therapy than metastatic lesions in soft tissues. The Council on Pharmacy and Chemistry (60) places the highest incidence of objective improvement on skull metastases. Pathologic fractures were observed to heal by Sylven and Hallbert (65) Karnofsky et al. (66), Nathanson and Kalley (67), Preston et al. (62), Watson and Fetterman (68). Godwin and Escher (69) and Prudente (63), have reported the regression of primary inoperable tumors to such an extent that surgery may be performed. Halberstaedter and Hochman (70), Lowenhaupt and Steinbach (71), Stoll (72), Taylor et al. (64), observe that the tumors of low grade malignancy.

appear to respond best to androgen therapy. Prophylactic testosterone to the point of masculinization is advocated by Loesser (52), Prudente (63), starting at the time of diagnosis of operable cases and continuing until reactivation occurs.

Estrogen therapy in advanced breast cancer is advocated in those women at least five years past the menopause, with two weeks to five months administration necessary before the drug can be considered of no value, by Adair (56), Herrman et al. (73), Nathanson and Kelley (67), Taylor et al. (64), and the Council on Pharmacy and Chemistry (60). The subjective improvements noted were relief from the pain of bony metastases, disappearance of dyspnea, anorexia and malaise, increased appetite, weight and optimism. While subjective improvement of osseous lesions is more frequent with androgen, the Council on Pharmacy and Chemistry (60), Garland et al. (74), and Stoll (72) state that objective response of metastases in bone are as frequent with estrogen as androgen. Estrogen appears to Edwards (75), Herrmann et al. (73), Mellors et al. (76), Nathanson and Kelley (67), Stoll (72), Taylor et al. (62), and the Council on Pharmacy and Chemistry (60) to have its most striking effect in improvement of soft tissue lesions. Primary tumors have been noted to become encapsulated by Haddow et al. (51), Herrman et al. (73), Nathanson (77), With Nathanson (77) reporting some primary inoperable tumors becoming operable, and

while he does not feel that this will produce a cure, he does feel it very worth while in longer palliation. Pulmonary metastases also have responded well in the experience of Adair et al. (56), Herrmann et al. (73), Nathanson (77), Taylor et al. (64), and the Council on Pharmacy and Chemistry (60), and in a series by Stoll (72), 12 of 25 patients were reported to show radiographic evidence of regression of tumor and/or pleural effusion.

In the comparison of various steroid preparations the Committee on Pharmacy and Chemistry (60) believes that methyl testosterone is as effective as testosterone propionate in comparable dosage, and that among the estrogens, ethinyl estradiol has shown slight superiority in effectiveness. It is also generally accepted that androgen is more universally effective, since it may be used at any age.

Opinion is divided on the duration of therapy, but the Council on Pharmacy and Chemistry feels that once steroid therapy is initiated the patient should be continued on full or maintenance dosage until recurrence takes place. A second remission may then be produced by using the alternate sex hormone, and they have even observed remissions occurring after the tumor became refractory to treatment with either hormone and all therapy stopped.

It is evident from the statistics of the Council also, that the steroids, while not curing cancers, are both making life more comfortable and adding some time to it. It is stated that

those benefited by treatment live about twice as long as those not benefited, and while this may be due to automatic selection, the further advanced patients not showing benefit, they feel that their figures will improve with time, since many of their patients are still being carried in remission.

Black and Speer (78) in cases of operable breast carcinoma note a 15% to 25% improvement in survival when androgen control is part of the primary treatment with radical mastectomy. However, they see the most improvement among the group in the three to five year group rather than earlier. They also show evidence that using both castration and antagonistic hormone together give better results than using either alone.

The mechanism of hormonal therapy benefit in breast cancer is yet unknown. Nathanson and his co-workers (67) feel that significant variation in the excretion of the "major steroid complexes" appear in patients under treatment, and are expanding this study to determine whether a mechanism of action may be discovered. As for the action on the cancer cell itself, the histological study of the Council on Pharmacy and Chemistry (60) has not yet revealed any evidence in change in the pathologic cell with hormone therapy. Nathanson and Kelley (67), Adair and Herrmann(55), Adair et al. (56), Godwin and Escher (69), Haddow et al. (51), and Herrmann et al. (73) all observe that with estrogen or androgen therapy the stroma

of cancer tissue is increased within which isolated groups of viable cancer cells with pyknotic nuclei and hydroptic cytoplasm are found. Nathanson and Kelley (67) interpret this to indicate that necrosis of the cells is affected by the hormone therapy, and that the increased stroma is a natural reaction to necrosis. Castration, which removes the primary source of estrogen, has been shown by McGavack (37) to have also an effect on the pituitary and adrenal cortical activity which may play a part in its effectiveness. Androgen is relatively increased by removal of the ovary if not absolutely by adrenocortical activity.

The non-specific actions of the hormones also must play an important roll in the responses seen. Such actions as mentioned in the first part of this thesis as sense of well-being, a favorable nitrogen balance, and a tendency toward better muscle tone, are antagonistic to the classic conditions described in the late cancer patient. It has been previously stated that the subjective response is far more frequently seen than objective response and may even be seen in patients in whom the tumor continues to progress during treatment.

From the experience of secondary benefit resulting from treatment of cases which show reactivation after either initial androgen or estrogen induced remission, the impression is created that it is not the specific hormone but a change in the hormone

balance that is effective. This impression is further supported by reports of secondary remission produced by dropping all hormone therapy when reactivation has taken place in spite of intensive hormonal therapy.

The apparently specific action of estrogen in the case of soft-tissue metastases as compared to androgen and bony metastases, is considered by Nathanson and Kelley (67) to be evidence of basic difference in action, the estrogen acting primarily on the tumor and the recalcification being a secondary phase, while androgen acting primarily as an anabolic stimulant produces recalcification without affecting the tumor. That soft tissue lesions are also benefited by androgen in postmenopausal women may be explained by Nathanson and Kelley (67) finding an increase in urinary estrogen excretion in these women on testosterone therapy.

According to the Council on Pharmacy and Chemistry (60), the side effects of hormonal administration are generally, except for hypercalcemia, not dangerous. There may be some concern for patients with low cardiac reserve about edema, and low salt diets are recommended with diuretics occasionally being necessary. Nausea and vomiting is frequently encountered early in the course of estrogen therapy but usually will disappear. If it is too severe to continue, a change to another estrogen preparation may eliminate it. Masculinization and increased libido are annoying

with androgen, but the benefits are so evident that most patients wish to continue the treatment.

In carcinoma of the male breast which has progressed beyond surgical reach orchiectomy is a very striking weapon and considered by Traves (79), Herrman (80), Leucutia (81), and Nathanson and Kelley (67) to be the treatment of choice. McCullagh (82) reports his best results in patients over 60 years of age. In Traves' (79) series of 13 patients, 10 were benefited. Reports of symptomatic benefits include marked relief of pain, a gain in weight, strength and appetite, and a feeling of well-being. Observations of objective improvement include regression of the primary and both lung and bone metastases. The reports of use of estrogen therapy vary, Nathanson reporting a case in which primary inoperable tumor regression allowed radical mastectomy and the patient showing no recurrence in four years. Ellis, et al. (83) report one case in which the tumor advanced rapidly, perhaps even being accelerated. The results of treating recurrences occurring after primary regression produced by orchiectomy also are unpredictable according to Nathanson and Kelley (67) and Traves (79), while Hines states that the use of either estrogen or testosterone may give a further period of regression in such cases.

Carcinoma of the prostate gland is another of the malignancies of older people that shows definite hormonal relations, the

original work being done by Huggins et al. (83) and From Hansen (85). Many clinical trials have shown that both estrogen therapy and castration are effective measures. Results with either method are similar according to Nathanson and Kelley (67), Karnofsky et al. (66), Marquardt and Flaherty (86), Nesbit et al. (87), however, castration produces the faster response with symptomatic relief within two to four days, while estrogen requires seven to ten days. Symptoms of urinary frequency, dysuria, pain, retention and hematuria are relieved early, with the objective improvement appearing after several weeks of treatment and including regression of both local and metastatic lesions. While the primary may remain quiescent, the metastatic lesions usually are the first to reactivate. Occasionally a primary tumor mass will not regress despite an otherwise favorable response, and in such cases Chute and Willets (88), Crane and Rosenbloom (89), Deming (90), Nesbit and Plumb (91), and Nathanson and Kelley (67) recommend surgical resection as a further palliative measure. It is usually considered that response of those tumors with elevated serum acid phosphatase is best. If widespread disease occurs without elevated acid phosphatase, the tumors are considered to contain non-secretory prostatic epithelium, which is so unlike the normal that poor response is expected from androgen control. Nesbit and Baum (92) reported, however, that they had 60% response to estrogen even if no elevated serum phosphatase

was present in cases with bony metastases.

There are instances mentioned of primary tumor masses inoperable due to local infiltration but no distant metastases evident, in which Gutierrez (93) feels that there is possibility for greatest benefit. He uses two months of treatment with 1.5 to 3 mgm. of stilbestrol and then if the lesion is responsive does a radical perineal prostatectomy. He feels that such cases are rare, but that the operability within this group can be raised from 10% to 80% by such treatment. Harrison (94) gives but one month of estrogen before surgery in such cases. Nathanson and Kelley (67) feel that the optimum time for surgery cannot be set in general but must be on the basis of individual response, using hormone until apparent stabilization at maximum regression of the lesion occurs. Scott and Benjamin (95) setting down criteria for surgery in such cases believe that above and beyond no evidence of distant metastases and apparent regression sufficient to permit reasonable assurance of complete removal they consider on this basis of general condition that a life expectancy of at least three years for the patient should be considered before surgery.

In the choice of treatment the speed of response, ease and freedom from medication that orchiectomy offers makes this method very desirable. Estrogens may produce gain in weight with female distribution, nausea and vomiting and enlargement of the

breasts, but these latter are usually not permanent or severe enough to necessitate discontinuance even if the same dosage is maintained. It is generally agreed that once started estrogen must be continued throughout life. Nathanson (96) states that by his probability calculations it is shown that a receptive tumor will respond no matter when hormone is started, and that the effects are limited regardless of when it is initiated. Nesbit and Cummings (97); Bumpus et al. (98), Stirling (99), Huggins (100), Dean (101), and Herger and Sauer (102) propose limiting hormone therapy to cases of advanced metastatic diseases. Alyea (103), Grand and Rosenbloom (89), Veit and Frazier (104), Deming (90), Harrison and Poutasse (94), and Wear and Schoenenberger (105) all feel that for maximum response hormone therapy should be started as soon as the diagnosis is made, regardless of whether metastases are evident. Harrison and Poutasse (94) propose using castration, estrogen and surgery together as the treatment, while Fergusson (106), and Wear and Schoenenberger (105) use initial surgery and estrogen, thus reserving castration until reactivation takes place.

Androgen control therapy is considered to prolong life by Nesbit and Cummings (97), Huggins (100), Veit and Frazier (104), Emmett and Green (107), Deming (108), Herbst (109), Riches (110), Scott and Benjamin (95), Gahagan and Fischman (111), and Nesbit and

Plumb (91) with the latter stating that the greatest survival improvement appears in the first 24 months. Nesbit and Baum (92) analyzing 1818 cases of prostatic carcinoma find that estrogen appears to give the better results when there are no metastases evident, but that in the case with metastases, orchiectomy was most effective, and also that the sooner the androgen control therapy was begun the better the result.

Huggins (100) and Scott and Vermeulen (112), in studying the excretion of estrogen, 17-ketosteroids and gonadotropic hormones before and after orchiectomy, noted that after the surgery there was a drop of androgens which later disappeared. They postulate that the source of androgen is the adrenal gland under increased stimulation of the anterior pituitary. These men and also Cox (113) have on this basis, in a few cases that have become reactivated after all other treatment, performed bilateral adrenalectomy, but although studies on survivors of the operation show that control of androgen is reestablished, the results on the tumor have been disappointing. In 10 cases that were unresponsive to orchiectomy and estrogen, Gahagan and Fischman (111) report that X-ray to the adrenal glands produced improvement in three cases.

Sprague et al. (114) have stated that cortisone will decrease the androgen production of the adrenal in man, and further that it will in rats produce atrophy of the adrenal cortex. Hayward

(115) noting this, used cortisone in a reactivated case of prostatic carcinoma. The patient, who had had resection of the prostate with orchiectomy in 1942, and was on stilbestrol and in remission until 1951, had developed severe pain from local recurrent tumor. The patient was soon dependent upon narcotics 24 hours a day for relief from pain and required constant care. Cortisone was given six days and then a dramatic improvement was described. For one year the patient has been using 25mg. of cortisone per day, and while he still has some pain occasionally he uses no narcotic, is up and about, and is engaged in constructive activities.

Using steroids other than estrogen to suppress endogenous androgen production is not new. Gutierrez (93) had reported progesterone effective in 1949 for certain cases refractory to orchiectomy and/or estrogen. Trunnell and Duffy (116) confirmed these observations on progesterone in 1950. The progesterone is given to suppress leutinizing hormone, which in the male, according to Albright and Elrick (117), is responsible for androgen production.

Deming (118) and Deming and Hovenanian (119) have shown by transplanting of human prostatic cancer that it will after eight generations in laboratory animals become independent of androgen and tolerant of estrogen. This autonomous state is considered to

be the basis of primary androgen control failures and terminal refractory reactivations.

Results of the use of the hormones in carcinomas arising from the other organs according to Nathanson and Kelley (67), have been disappointing. A report by Lemon and others (120) indicates that in a case of carcinoma of the thyroid in a 53 year old woman, metastatic lesions of vertebrae were relieved. The metastatic lesions had become refractory to X-ray and radioactive iodine uptake was not sufficient for therapy. Estrogens were tried but made the condition worse. Testosterone therapy produced relief and showed maintained benefit for 14 months, the patient having been bedfast before treatment but returning to housework three months after therapy started. Recalcification occurred in both irradiated and non-irradiated lesions.

Testosterone therapy in a case of carcinoma of the uterine body with pulmonary metastases was reported by Freed and others (121) to have relieved the symptoms of the pulmonary lesion, and caused regression of the metastases to such an extent that they could no longer be seen by X-ray.

Hines(53), Nathanson and Kelley (67), and Pearson and Eliel (122) in their discussions of the hormone treatment of cancer agree that the adrenal cortical hormones are generally to be avoided in cases of malignancy except for acute myelogenous

leukemia, acute and chronic lymphatic leukemia, Hodgkin's disease, and multiple myeloma. Of these conditions only chronic lymphatic leukemia and multiple myeloma are seen in the older age group according to Harrison (123). Even in these diseases hormone therapy offers only temporary relief, usually less in the older patient than in younger, and for this reason is used as a last effort after all other therapeutic methods have either failed or become ineffective.

Administration of ACTH, according to Pearson and Eliel (122) produces a marked destruction of both normal and lymphoid tissues in patients with chronic lymphatic leukemia. When the dietary intake of these patients was doubled the catabolic effects of the drug were overcome both for the normal and neoplastic tissue. Testosterone when administered alone showed no effect on the neoplastic tissue, but an anabolic effect in the normal tissue was noted. However, using testosterone and ACTH at the same time produced the desired catabolic effect on the neoplastic lymphoid tissue, but at the same time an anabolic systemic effect. In his studies the leukemia patient was benefited by Compound F, but not as much as with ACTH. There was no change in the condition when Compound A acetate was used.

Burnstein (124) was reported a series of 300 cases in which he has used the steroid hormones as a supplementary weapon

In the treatment of diabetes Mellitus. The men selected were all older so the damage to spermatogenesis was not a contraindication to the administration of testosterone. The women given estrogen were not excluded from the series for reasons of age. His overall results show that two-thirds of the patients could reduce their insulin requirements. The aim is, of course, substitution of sex steroids, which may be given orally, for insulin which must be administered parenterally. The report shows no instances in which complete elimination of insulin was accomplished on his experimental dose schedule which was always given for three months, then placebos were given to check the return of increased insulin requirement. Schoene (125) in his article on osteoporosis noted that three of his female patients who had diabetes showed a reduced insulin requirement while on testosterone therapy.

Albright (126) described senile osteoporosis as distinguished from osteoporosis of disuse or post-menopausal osteoporosis. His theory is that it is a direct result of decreased production of protein anabolic steroids. The effect of testosterone in these cases is probably both inhibition of the protein anti-anabolic S hormone and the direct protein anabolic activity, as well as indirectly by increasing the serum albumin level and thus aiding bone matrix production. Schoene (125) recently reported a series of thirty cases (28 women and 2 men) of senile osteoporosis.

treated by intermittent testosterone therapy limiting each patient to a decreasing schedule over twelve weeks and followed by four weeks of rest period. Treatment was repeated if pain recurred. Minimal side reactions occurred. The pain was usually relieved in three weeks and he reports all patients were generally benefited, becoming more animated and having a sense of well-being. The longest treatment was one year, most cases requiring three to six months.

Ischmael (127) describes osteoporosis as one of the most common primary factors in the etiology of degenerative arthritis. While the condition may be the result of trauma alone or a disease process alone he considers the majority of cases to be an intermediate group which are the result of traumatic breakdown of previously damaged or vulnerable joint structures. He uses testosterone and estrogen together in all cases where by history the symptoms date from the menopause or if there is radiologic evidence of demineralization. The steroid therapy results are reported as excellent in controlling symptoms and the patients are encouraged gradually to resume activity as tolerated. Orthopedic principles must also be observed to minimize abnormal stresses, and physiotherapy is used if necessary.

Connolly (128) states that if osteoporosis is present fracture healing is aided by estrogen administration. Schoene (125) and others have considered the sex steroids of benefit in the healing of fractures. Deatson et al. (129) however, have made a study

of animal bones healed with and without estrogen administration during the healing period and concluded that they could find no benefit in roentgenographic changes, blood chemistry, weight gain or breaking strength of the healed bones in the animals given hormones. Their series was conducted however with normal dogs. Hill and Weinberg (130) contend that giving of estrogen will retard callus formation in bone repair. Portugal et al. (131) describe a general suppressive effect on granulation tissue formation from both testosterone and estrogen. This effect they say is the result of both a direct local action and inhibition of the pituitary growth hormone. The latter theory of action being supported by evidence of a rise in eosinophils noted by Sackler et al. (132) in patients on combined estrogen testosterone therapy.

It would appear then that any aid to the healing of fractures from the administration of sex steroids is questionable. It is almost certainly limited to those in whom there is a pre-existing osteoporosis and the therapy may actually delay callus formation.

Foldes (133) recommends the sex steroids in the preparation of older people for surgery, stating that there is clinical evidence of benefit. The patients show the well-known response with euphoria and increased muscle power and also the androgens are said to produce an increased functional ability of the urinary bladder. These hormones are continued in the post-operative period because of their ability to maintain not only subjective sense of vitality

but objective evidence in increased food intake, better kidney function, increased plasma protein, and apparent hastening of recovery. No mention is made of any incidence of delayed healing due to suppressed granulation tissues. He also recommends that adrenal cortical hormones be used during surgery and in the immediate post-operative period, stating that a more favorable response to anesthesia is thus obtained. Shock and Solomon (134) pointed out by a study of the response to stress that although the pituitary-adrenal cortical relationship was intact and the pituitary is able over the long term to secrete normal amounts of ACTH, there was in older people an abnormally prolonged lag between the onset of stress and the response, thus in this period, cortical hormones are of value.

In the treatment of senile vaginitis with atrophic changes in the vaginal mucosa, McLane (135) using dienestrol in a cream base has reported a series of 123 patients. For classification as successful treatment only those with both clinical response and relief of symptoms were used. This group being 68.3% of the series. Another 25% had symptomatic improvement but no clinical improvement seen in the vaginal mucosa. Therapy was over one to three weeks with 0.446 mg. dienestrol used nightly in 4.46 gm. of cream (1:10,000).

Believing that psychotic disease is related to a metabolic disorder which manifests itself by abnormal functioning of the nervous system, the Sacklers and others (132) set about using sex steroids as therapeutic agents. Their patients were mostly younger, but their

work is significant in all age groups. They attempted treatment only on patients who had been completely worked out as to diagnosis, including schizophrenia, manic depressive psychosis, involuntional melancholia, some having been refractory to electric shock therapy. Although the best result was in the age group 16 to 25 years, the next best group was the over 50 year group with 4 of 17 (24%) reaching convalescent status. It was indefinitely shown that those who had been in the institution less than 6 months were more favorable candidates which may be the reason that the older group did not have more attaining convalescence, yet they did better than any group between 25 and 50 years. Previous refractoryness to EST was shown to be unimportant as a factor. The degree of help correlated with the peak of eosinophiles and a greater lymphocyte-neutrophil ratio indicating that therapy was most successful when adrenocortical activity was most strongly counterbalanced.

The authors conclude that the sex steroids may bring to the management of psychotic disorders an efficient treatment, pleasant both for physician and patient.

Newman (136) reports a series of female patients with anxiety and tension states which she subdivides into two categories. There were those whose vaginal cytology indicated hyperestrogenism in which androgen was used alone. The other group who showed hypo-ovarianism by cytology or were having menopausal symptoms were treated first with estrogen alone without relief of the

tension, but when given estrogen-androgen combined therapy showed "excellent results". All androgen doses were less than masculinizing and oral medications were used. It is not known upon what basis the success of her treatment was judged.

Summary

The sex hormones have long been associated with aging and more recently, because of a striking similarity of the symptoms of Cushing's syndrome and the degenerative diseases of aging and the finding of adrenal cortical hyperplasia or adenomata in significant numbers of older people, the adrenal cortex has appeared as an important etiologic factor in these conditions. Recent availability of the hormones in pure form has accelerated the clinical tests which have shown many promising results. Certain of the degenerative changes associated with aging can be reversed, and there is promise that the desirable effects of the hormones may be retained while eliminating the undesirable actions from hormone products of the future. The protein anabolic action of estrogen and especially androgen causes a striking reversal of the negative nitrogen balance seen in many older people. There is also evidence of some psycho-somatic lift from the sex steroids which is not only a euphoria, but influences the creative output of these patients. The sex steroids are powerful growth and anabolic stimulants which, because certain organs may be over-stimulated while others may be refractory, thus use of them for rejuvenative purposes should be made with caution.

These steroids have been shown to have a specific action

in many of the conditions seen in older patients. The various symptoms of the menopause are relieved by their use, generally combined estrogen androgen therapy being most satisfactory.

Malignancies of the breast and prostate and metastatic lesions of some other tumors are benefited by sex steroid therapy. Remissions in the progression of chronic lymphatic leukemia are produced by combined ACTH and testosterone. Surgery remains the only hope of cure in those cases of malignancy which are not too extensive to permit complete removal. Steroids do, however, extend the life of patients with inoperable, recurrent or metastatic malignancies and make them more comfortable.

While diabetes mellitus cannot yet be controlled by oral administration of sex steroids rather than insulin injections, the requirement of insulin is reduced in diabetic patients on hormone therapy.

Sex steroids especially testosterone are effective agents in remineralization of the bones of older people which is of benefit in osteoporosis and in degenerative arthritis, and fracture healing when osteoporosis is a complication in such cases.

The condition of older candidates for surgery is improved by the use of hormones pre-operatively and recovery is aided and the danger of shock lessened by their use during and after surgery.

Certain psychotic patients have been benefited by a course of sex steroid therapy indicating that early use of this treatment

may be pleasant and efficient method of rehabilitation.

Conclusions

1. Some of the degenerative processes of aging can be reversed, but as yet there remains the threat of over-stimulation of tissue growth and activity of the patient by use of steroids for this purpose.
2. Therapy directed toward counteracting adrenal cortical hyperactivity shows promise of being an effective measure to combat the degenerative diseases of aging.
3. The anabolic effect of the sex steroids is effective in reversing the negative nitrogen balance of older patients and promoting remineralization of bone.
4. Severe menopausal symptoms are relieved by steroid therapy.
5. As a palliative measure in late malignancy of the breast and prostate and in chronic lymphatic leukemia the steroid hormones offer extended life and relief of symptoms.
6. There is evidence that the use of the steroids early in the treatment of psychoses may offer an efficient means of treatment.

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