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Delta 5 pregnenolone in the treatment of rheumatoid arthritis

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DELTA 5 PREGNENOLONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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INTRODUCTION

The dramatic effect of cortisone and pituitary adrenocorticotropic hormone (ACTH)[1,2] in the treatment of rheumatoid arthritis and other collagen diseases has stimulated further research to determine the activity and possible application of other steroid hormones in this disease.

Previously our knowledge of the remissions seen in rheumatoid arthritis has been limited to the study of unpredictable and indefinite cases of remissions associated with pregnancy, hepatitis with jaundice, and occassionally with the administration of gold. ACTH and Cortisone have made it possible to study clinical and laboratory changes from active disease to remission in the space of a few days, thereby suggesting that there is a definite remission factor present and that it is common to all cases of rheumatoid arthritis.

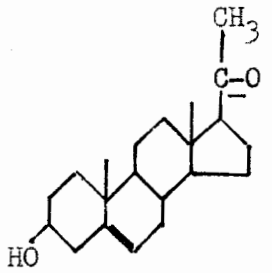
Of the steroids now being studied, delta-5-pregnenolone appears to have certain advantages because: (a) its possible role as a precursor of more active steroid hormones [3,4]; (b) its beneficial effect on fatigue [5]; (c) its sparing action on the adrenal cortex [5]; (d) its lack of toxicity in animals [6,7,8] and man [9,10]; (e) it has not shown any adverse effect on endocrine physiology [11]; (f) it has shown some promise in the treatment of rheumatoid arthritis [12,13] and, (g) its efficacy by mouth [3,5] has decided advantages to the patient over parenteral administration.

HISTORY

Pregnenolone was first prepared chemically by Butenandt[14] in 1934, and was obtained by extraction from hog testes by Ruzicka [15] in 1943. Several early investigators tested it in animals for estrogenic, progestational, and adrenocortical activity, but none was found in the range of dosage used [14,16,17,18]. But with considerably larger amounts, Selye [3] was able to elicit a variety of effects in animals, the more important of which were a favorable influence on spermatogenesis and a protective action against damage to the testis induced by estradiol. Hoagland [19] was the first to report a demonstrated physiologic activity in man, he found a reduction in the urinary excretion of 17-keto-steroids when this was elevated as a result of fatiguing activity. Davison and Koets [12,13] used this fact as a clue to the management of ankylosing spondylarthritis (Marie-Strümpell) and rheumatoid arthritis, and obtained clinical benefits in these diseases sufficiently encouraging to warrant further investigation.

CHEMISTRY

Delta-5-pregnenolone is delta-5-pregnene-3-beta-ol-20-one. It is a steroid, the 3-hydroxy analogue of progesterone, appearing in the penultimate stage of the oxidative preparation of progesterone [20,21,22,]. The empirical formula is $C_{21}H_{32}O_2$. The structural formula is shown on the next page. The melting point is 190 degrees centigrade [14,22,23,24,25], or 186-187 degrees centigrade [27], or 192-194 degrees centigrade [28]. Optical rotation is $(\alpha)^{26}_{D} = +35 \pm 4$ in absolute alcohol [29], $(\alpha)^{18}_{D} = +30 \pm 2$ in absolute



alcohol [28].

When pregnenolone is crystallized from benzene or alcohol-acetone, it occurs as white, opaque crystals which are tasteless, and odorless. It is insoluble in water and slightly soluble in most solvents except propylene glycol and mixtures of propylene glycol and water.

Purity is determined by melting point and optical rotation.

Identity is determined by characterizing pregnenolone as either itself, the acetate [23,28], methyl ether [16], 17-bromo-e-acetate [30], or the oxide [31].

Storage of pregnenolone entails no difficulties, either in the dry form or in solution in propylene glycol or sesame oil: the compound is stable, and requires no special precautions [11].

TOXICITY

Toxicity in animals. In mice, no toxicity could be found even in oral doses up to 5 Gm. per Kg. of body weight, no symptoms or deaths were produced [11].

Three experiments failed to disclose a toxic action of pregnenolone in rats [11]. They were: (a) oral administration (in starch) of 1 Gm./Kg. three times weekly for 50 doses; (b) intraperitoneal injection (in saline suspension) of 0.2 Gm./Kg.

three times weekly for 50 doses; and (c) oral administration in the food, 0.01 and 0.1 Gm./Kg., daily for three months. In studies (a) and (b), no change was observed in the red blood cells, hemoglobin, white cell count or weight of viscera, and in (c) there was no difference in growth rate, food intake, fertility, or size and condition of litters, when the treated animals were compared with controls.

Male and female albino rats receiving 0.01 Gm./Kg. subcutaneously daily for three months showed no change in the weight of the several viscera [32].

Toxicity in man. So far, the evidence suggests minimal toxic action in man following parenteral or oral administration of pregnenolone, which is comparable with the experience in animals.

Only two cases of toxicity have been reported. Tyler et al [33] in their study of 25 men receiving an oral dosage of 25 to 75 mg. daily and intramuscular dosages of 5 to 20 mg of pregnenolone or pregnenolone acetate, stated: "One patient was started on 50 mg. per day orally, but after a week had a diffuse erythematous skin eruption which he had not experienced previously, and the medication was discontinued, following which the eruption disappeared; thus it must be assumed that this was a mild toxic reaction. No other significant untoward reactions were reported to us by the patients." Cohen et al [34] reported: "Of the 20 patients treated with pregnenolone....treatment was discontinued in one, who showed allergic swelling of the lips,...."

Pincus and Hoagland [5,9,10,19] report with doses of 25 to 100 mg. daily: "Finally we should like to point out that we have encountered no deleterious results in connection with the ingestion of delta-5-pregnenolone in our studies involving several hundred men and women who have taken the medication; in some instances in doses of 100 mgm. per day for as long as four months. The substance is nontoxic."[9]

Davison et al [13] reported with doses of 100 to 300 mg. of pregnenolone daily over a four month period in 12 patients: "No evidences of toxicity have been observed from prolonged administration of pregnenolone."

Freeman et al [35] used from 300 to 700 mg. of pregnenolone daily in 30 patients, the average dosage being 500 mg. orally for an average of six weeks. They reported: "No toxic effects were noted."

The possibility of side actions due to the prolonged parenteral administration or oral ingestion of pregnenolone in large doses cannot be excluded. One anticipates, however, that any such side actions are likely to reflect alterations in physiology, rather than outright toxicity as in the case of pharmacologic compounds. None of the known activities seems to suggest a disturbance to be anticipated with intensive use, save the peculiar anesthetic action of all steroid hormones in massive dosage [36,37].

PHARMACOLOGY

Pregnenolone has few pharmacologic actions, if any, which are not hormonal in character, such as effects on the pituitary glands and sex organs, and interactions with other hormones.

An anticonvulsant action against metrazol and against electrically induced convulsions in the cat was reported by Henderson et al [11].

Blood chlorides were persistently raised by pregnenolone according to a report of Selye [3], while Weissberg et al [38] in a study of 11 patients using doses ranging from 100 to 400 mg. report that there is "....a slight tendency to retain sodium and chloride."

Hoagland and Stone [39] reported that tissue potassium (of brain and muscle) was unaffected in normal rats by the administration of 0.0035 Gm./Kg. of pregnenolone but was reduced in adrenalectomized rats. Weissberg et al [38] report in their study of 11 patients that there was a trend to develop a negative balance for potassium.

Weissberg et al [38] also reported the trend to develop a negative nitrogen balance in their 11 patients receiving 100 to 400 mg. of pregnenolone. Reifenstein [40] stated that the nitrogen balance was only slightly or not significantly improved by a dosage as low as 30 mg. per day, intramuscularly, for eighteen days, in a patient with postmenopausal osteoporosis. Abels et al [41] said that in one person the administration of 100 mg. daily for thirty-six days was described as leading to an increase in plasma proteins, but the circumstances of the study (route of administration, underlying diagnosis, effect on nitrogen balance, etc.) are not disclosed in the article.

HORMONAL ACTIONS

Selye and other workers have done a large amount of experimentation using large doses of pregnenolone in animals, for the most part in rats. Their results, however, were not the same as those found in human clinical experience. Henderson et al [11] have summarized the findings for their possible theoretic value under the headings: pituitary, testis, secondary sex organs, pregnenolone and other hormones (progesterone, androgens, estrogens, gonadotropins), anesthetic action, kidney, adrenocortical activity, and others.

Henderson concludes: "These diverse data make it possible to ascribe a variety of the classic hormonal actions to pregnenolone, but it should be recognized that the actions are elicited only under unusual experimental conditions and at high dosage, and even then are not of outstanding intensity. Hence it may be confusing, at best, to view this substance as a 'gonad-protecting' or 'gonadotropic' hormone or as another 'male sex hormone'. That such a variety of the customary hormonal actions can be elicited in some degree with a substance that appears actually to be devoid of all of them would imply that such experiments as have been cited do not serve to screen a compound, the action of which does no fall within any pattern thus far recognized. Likewise, the conception that pregnenolone operates by being first converted into some more familiar steroid hormone is not well borne out by the findings to date: the extent of conversion would need to be meager, and the end-product somewhat different in each experiment." [11]

Davison et al [13] reported with doses of 100 to 300 mg. of pregnenolone daily in 12 patients over a four month period: "There has been no elevation of the fasting blood sugar and no edema. There has been no effect on the menstrual cycle, the duration of menstruation, or its character in any of the women who have recieved it."

Pincus and Hoagland [5,9,10,19] found when 50 mg. of pregnenolone was administered daily orally or parenterally that the urinary elimination of 17-ketosteroids could be reduced.

CLINICAL STUDIES

Several clinical applications of pregnenolone have been studied on an empirical basis.

Fatigue and Endurance. An early application was related to fatigue and endurance. Hoagland [19] showed that fatigue, produced by a standarized method which simulated the operation of an airplane in flight, was objectively measurable in terms of the urinary elimination of 17-ketosteroids. The elimination of 17-ketosteroids could be correlated with the number of errors made in tests, with time actually spent in the air, or with anoxia, in that the more stressed activity was reflected in a higher excretion. Fatigue was found to induce an increase in 17-ketosteroid excretion which could be plotted on a line of given slope. When pregnenolone, 50 mg. orally per day was administered, the slope of this plot was reduced to one-half its original value. Pregnenolone was further described as improving the scores obtained in test runs, and as leading to a diminution

in the feeling of fatigue. Pincus and Hoagland [5,9,10] in further studies on fatigue and endurance concluded that pregnenolone had a cumulative effect, its effect being evident for several days afterward, consisting of an obvious improvement in performance. Graham-Bryce et al [42] with six patients tried to duplicate the work of Pincus and Hoagland [5] (with 14 patients) in evaluating the effect of 50 mg. of pregnenolone orally daily on performance using a target meter but they were unable to confirm any aspect of the previous findings [5]. Graham-Bryce et al [42] attributed the discrepancy in part to the absence of stress in the performance of their test subjects and personal motivation was recognized as an improtant variable so that seemingly comparable studies might yield distinctly opposed results if one group felt obliged to succeed, while the other merely performed the work.

Spermatogenesis. Tyler et al [33] gave pregnenolone or pregnenolone acetate orally or intramuscularly for periods up to twenty weeks to 25 patients having oligospermia (less than 60 million sperms per cc.), poor motility, or high proportions of abnormal sperms, using in most instances 50 mg. daily by mouth or 10 to 20 mg. daily intramuscularly. Although in a few cases there may have been improved motility, and at least one patient had a higher sperm count after treatment, the results, on the whole, with these dosages, were not considered to be of any significance.

Abarbanel [43] since September 1947 has treated 50 patients with oligospermia with pregnenolone. Semen was judged inadequate

if there was oligospermia (less than 30 million sperms per cc. on three or more occasions), motility poor (motility of 20 per cent or less in four hours and/or 10 per cent or less in eight hours after ejaculation), or abnormal sperm heads were high (21 per cent or more abnormal sperm heads). Pregnenolone was administered intramuscularly either in oil or in aqueous suspensions in doses from 40 to 400 mg. a week, the average being 200 mg. a week. Injections were given twice a week for twelve weeks, followed by a rest period of four weeks. The successive series were given for a period of up to two years. There were 15 cases in which pregnancy occurred. Most of the men did show an improvement in the quality of the semen, increased duration of active motility usually being first to occur, followed by a not infrequent increase in count. He states: "....no definite conclusion as to the manner by which pregnenolone improves the quality of semen seems apparent at present. Whether it is a indirect constitutional one or a direct gonadal one or a combination of both requires further study. At the present time it is suggested that in some manner the fertilizing capacity of the sperm is probably enhanced." [43]

Myasthenia gravis. Henderson et al [11] report: "Six patients obtained no benefit from pregnenolone."

Hypertrophic arthritis. McGavack et al [44] report that 6 of 8 patients with hypertrophic arthritis showed slight improvement.

Lupus Erythematosus. "Two patients with lupus erythmatosus were markedly improved, both as regards their sense of well-being and the skin lesions." [44]

"One young woman with a diagnosis of disseminated lupus was given 300 mg. of pregnenolone aqueous suspension daily for two weeks. The articular symptoms were slightly improved and the swelling was reduced, but she was so greatly emaciated and had so little muscle into which the material could be injected that injections were discontinued." [13]

Malignant exophthlmos. "One case of malignant exophthalmos was markedly relieved." [44]

Addison's disease. "Four patients with Addison's disease obtained slight improvement, but in no instance was this as marked as with desoxycorticosterone or with desoxycorticosterone plus testosterone." [44]

Other Diseases. Other conditions in which the drug has been tried are erythema nodosum, hypothyroidism, hypothalamic obesity, and diabetes mellitus with dermato-myositis.[44]

RHEUMATOID ARTHRITIS

Henderson et al [11] reports that J. Landsbury in a personal communication in December 1946 suggested the use of pregnenolone in the treatment of rheumatoid arthritis. Then in March of 1947, J. Landsbury in another personal communication reported the oral use of pregnenolone in three cases of rheumatoid arthritis. "In three cases of rheumatoid arthritis there was subjective improvement with less fatigue, a gain in strength,

less pain, and in two cases an actual measurable reduction in swelling. In one case there was relief of a constant dull pain in the eyes which had been present for many months and a relief of nervousness and an increased ability to sleep so that sedation could be discontinued. In considering these effects, I feel that there is a suggestive lead here. There is no evidence that pregnenolone is curative but I think further trial is justified." [11]

Davison et al [13] used pregnenolone and pregnenolone acetate intramuscularly in doses from 100 to 300 mg. daily in thirteen patients with rheumatoid arthritis, and 12 patients with spondylarthritis. "The synthetic steroid delta 5 pregnenolone, administered by intramuscular injection in adequate dosage, effects remission in rheumatoid arthritis. When it is withdrawn, symptoms and signs of active disease return, usually within a few days." Their experience indicated that the effective daily dose was 200 mg. and that after the symptoms have been relieved, reduction in dosage to 100 mg. daily was sufficient to maintain the benefits. In those having arthritis affecting the extremities, they found relief of stiffnes and pain, great improvement in muscle strength, relief of fatigue, and a feeling of well-being, usually within a week and sometimes within three of four days. Reduction in joint swelling, especially if there were large effusions, was slow, and reduction of the sedimentation rate, if any, did not parallel clinical improvement but followed it.

Freeman et al [35] report: "A total of 30 patients with rheumatoid arthritis of varying degrees were given pregnenolone or pregnenolone acetate orally for an average of six weeks, the dosage averaging 500 mg. daily. Fifteen patients experienced striking relief; 11 patients showed a mild degree of improvement, and 4 patients did not obtain improvement. Of 16 subjects in whom treatment has been discontinued, improvement has been maintained an average of six weeks."

Both Davison and his workers and Freeman and his workers used pregnenolone alternately with placebos in some patients and found a tendency to relapse on placebo medication with resumption of improvement on pregnenolone therapy.

Cohen et al [34] have used delta 5 pregnenolone on 20 patients with rheumatoid arthritis in dosages of from 0.3 to 12.0 gm. over periods from one to 131 days. Of the 20 patients treated, 12 were markedly improved, three slightly, two showed no improvement, one had one injection, and treatment was discontinued in one, who showed allergic swelling of the lips, and in one who developed an abscess at the site of injection. "Several patients responded to therapy immediately and dramatically. Uniformly, swelling and pain were relieved promptly, and activities impossible for years were engaged in. Present usual dosage is 300 mg. intramuscularly daily. Several patients have continued on this regimen for more than 40 days with no toxic or untoward reactions, except for one allergic case, which was probably due to the menstrum. Three patients have maintained improvement on doses of 300 mg. administered twice weekly."[34]

Cohen and McBride [46], in an editorial, stated that they had used pregnenolone in nearly 300 rheumatoid arthritics, 75 per cent of whom have shown definite subjective and objective improvement.

Guest et al [45] gave intramuscular injections of pregnenolone or pregnenolone acetate to nineteen patients in course of 7 to 51 days. The dosage varied from 100 to 300 mg. given two or three times a week to daily injections. They state: "With one exception there was no consistent subjective or objective improvement in any of the patients treated."

Stock and McClure [47] gave intramuscular injections of pregnenolone in oil to one case of ankylosing spondylitis and to nine cases of rheumatoid arthritis. They gave an initial dose of 300 mg., followed by 200 mg. daily for three weeks. At the end of this period they gave injections of oil containing no pregnenolone daily for 2 weeks. A second period of pregnenolone injections were then started, and this time the pregnenolone was given in combination with ascorbic acid (1 g.) and hyaluronidase (1000 units),for two more weeks. They state: "Objective improvement was evident in the case of ankylosing spondylitis and in two of the cases of rheumatoid arthritis. In 2 of these 3 cases, however, it is questionable whether the improvement can be attributed to the pregnenolone therapy. Local reactions occured in seven of the cases ans were severe in five."

Polley and Mason [48],in a study of 12 steroids, gave pregnenolone in daily doses of 100 to 300 mg. intra muscularly for a total of 2.6 Gm. in 10 days to a patient with rheumatoid

arthritis. They state: ".... a slight degree of subjective feeling of well-being occurred during the administration of this substance but there was no significant degree of objective improvement in the rheumatoid arthritis."

SUMMARY

Pregnenolone is a steroid having pharmacologic and hormonal behavior which has not been satisfactorily characterized within any definite or familiar framework. Several slinical applications of pregnenolone have been studied, on an empirical basis, and have provided some interesting results in fatigue and endurance, spermatogenesis, hypertrophic arthritis, lupus erythematosis and rheumatoid arthritis.

It has an exceptionally low order of toxicity.

A fair proportion of rheumatoid arthritics receiving pregnenolone in sufficient dosage, for an adequate period, show symptomatic changes sufficient to warrant further study.

Comparison of one form of therapy with another can be made on a definite mathematical basis if groups of comparable and adequate sized are selected. It is obvious that when Tables 1 and 2 are compared that there is not a sufficient amount of data compiled on pregnenolone in the treatment of rheumatoid arthritis, but it does indicate that further study is warranted.

It may be that opeimum therapy for rheumatoid arthritis may be a combination of gold with certain steroids.

TABLE 1

Results of Pregnenolone Therapy

Author	No. Pts.	Dose	Improvement			
			Marked	Moderate	Slight	None
Henderson [11]	3		2		1	
Davison [13]	25	100-300mg.	10			
Freeman [35]	30	500 mg.	15	11		4
Cohen [34]	20	300-1200mg.	12		3	2
Cohen [46]	300		75% showed improvement			
Guest [45]	19	100-300mg.	No consistent improvment			
Stock [47]	10	300mg. Init. 200mg. Daily		3		
Polley [48]	1	100-300mg.		No improvement		

Table 2

Results of Chrysotherapy in the United States [49]

Author and year	No. of pts	Years of follow-up	Remission or great improvement %	No improvement %	Relapses %	Toxic Reactions %
1936 Oren	66	0	91	9		
Phillips	9	0	0	7		100
1937 Sashin, and Spanbock	22	½	54.7	20.6	7.4	11
1939 Key, Rosenfeld, Tjoflat	53	-	40	15		
Sashin, Spanbock, Kling	80	1-5	43.2	17.2	10.4	23.7
Snyder, Trager, and Kelley	50	2	12	52		17
1940 Tarsy	22		54.5			36.6
1941 Logefoil & Hoffman	74	1 - 5	65	14.7	13.7	
Gardner	250	1 - 5	70-80			
McCarty	36		78	22		
Smyth & Freyberg	80	½ +	61			33
Thompson & Wyatt	26		61.3	37.6		
Dawson, Boots, & Tyson	100	½-2	51	15	12	50
Tarsy	36		52.6	25		
1942 Cecil, Kammerer, & DePrume	245	1 - 5	66	14	40	42
Furlong	14		9	2		
1943 Traut & Barton	14		0			50
Hartung	264	1 +	54		21	
Price and Leichtendtritt	101	1-3	60	39	39	38
Winkler	32		4			
1944 Rawls, Gruskin, Ressa, Worzan,& Schreiber	100	1-4	53	14		42
Stengel	30		57	10		
1946 Ragan &Tyson	142	3-6½	50	11	75	30
Short, Beckmen, & Bauer	35	4-5	20	40	43	29
Waine, Baker, & Mettier	58	3½	57			50
Oren	150		84.5	15.5		
1947 Browning,Rice Lee, and Baker	47	1½-6½	23	62	4	62
Rose	91	1 +	73	11		11
1948 Cohen, Dubbs, & Goldman	475	1-5	64	10		21
1949 Kling,Sashin, and Vento	455	1-5	51.4	12.1	17-75	36

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