URINARY EXCRETION OF 17-HYDROXY-20-OXOSTEROIDS IN NORMAL HEALTH AND IN RHEUMATOID ARTHRITIS

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In the course of their outstanding investigations into the urinary excretion of steroids, Dobriner (1951) and Dobriner and others (1951) reported the isolation of 17- α -hydroxypregnanolone (I) from the urine of four out of five patients with rheumatoid arthritis. The daily excretion of this compound (I) recorded for one patient only amounted to 1.5 mg. The authors also reported the absence of (I) from the urine of healthy persons, and its excretion by patients with adrenal hyperplasia and adrenal tumour (Lieberman and Dobriner, 1945; Mason and Strickler, 1947; Miller and Dorfman, 1950), and they concluded that the excretion of (I) in the investigated cases of rheumatoid arthritis pointed to an adrenal dysfunction. More recently Lieberman and others (1954) have detected (I) in a pregnancy urine (0.07 mg./l.), and Dobriner and others (1954) have found it in a case of myelogenous leukaemia (0.5 mg./day), and have noted that small amounts of (I) are found also in normal urine. In view of the latter finding, (I) cannot be considered any longer to be a "pathological" steroid, but its excessive excretion may reflect a derangement of steroid metabolism, as in the adrenogenital syndrome (Jailer, 1954; Appleby and Norzymski, 1955). The information available is insufficient to decide whether rheumatoid arthritis is associated with a metabolic defect manifested by abnormal levels of (I) in the urine. The purpose of the present report is to record some new data bearing on this problem.

(I) contains a molecular fragment which is uncommon among urinary steroids (Figure). This fragment comprises carbon atoms 17, 20, and 21, of which C₁₇ is substituted by a hydroxyl group, and C₂₀ by an oxo group, and C₂₁ is unsubstituted. The class of compounds sharing this structural feature may be termed 17-hydroxy-20-oxosteroids unsubstituted at C₂₁, or 21-deoxy-17 : 20-ketols, or briefly 21-deoxyketols. Appleby and Norzymski (1954,

1955) have recently developed an analytical method for the group determination of such compounds which consists in their selective conversion into 17-oxosteroids (17-ketosteroids) and measurement of the latter by means of the Zimmermann reaction. This method has now been applied to the determination of urinary 21-deoxyketols in normal health and in rheumatoid arthritis.

Figure.—Chemical formula of 17- α -hydroxypregnanolone (I).

The investigated group of subjects comprised 26 healthy persons (12 men, 14 women) and 26 patients with rheumatoid arthritis (11 men, 15 women). In one patient the disease was in its early acute phase; in all others the condition was chronic, though of varying duration and severity. Concurrently with the assays of 21-deoxyketols, determinations were performed of 17-ketogenic steroids (17-KGS; Norzymski, 1952; Norzymski and others, 1953;

TABLE
RESULTS OF STEROID ASSAYS

Group	Sex	Subject No.	Age (yrs)	17-KGS* (mg./day)	17-OH CS* (mg./day)	21-deoxyketols*	
						(mg./day)	Mean
Normal Health Average age 36	Women	1	22	12.6	12.6	0.16	0.14
		2	22	11.8	12.3	0.32	
		3	23	17.2	16.1	0.19	
		4	23	5.6	5.7	0.10	
		5	23	10.0	13.7	0.10	
		6	25	14.6	14.0	0.17	
		7	25	16.0	15.9	0.27	
		8	28	6.2	8.1	0.07	
		9	31	8.2	7.8	0.11	
		10	40	12.5	11.9	0.08	
		11	44	—	17.4	0.15	
		12	53	—	13.3	0.03	
		13	62	—	12.4	0.06	
		14	70	—	12.5	0.11	
	Men	15	16	11.0	10.4	0.21	0.26
		16	18	13.1	16.5	0.25	
		17	24	13.0	10.6	0.20	
		18	26	9.6	12.9	0.20	
		19	31	13.8	—	0.40	
		20	35	15.6	17.2	0.46	
		21	37	12.9	13.9	0.25	
		22	43	9.0	9.6	0.20	
		23	46	7.2	6.2	0.34	
		24	51	—	13.7	0.28	
		25	53	13.2	13.2	0.14	
		26	57	—	7.4	0.13	
Rheumatoid Arthritis Average age 51	Women	27	26	7.8	8.4	0.18	0.15
		28	29	—	7.5	0.16	
		29	39	8.0	9.6	0.31	
		30	42	7.2	6.2	0.18	
		31	50	8.4	8.2	0.30	
		32	50	8.6	8.6	0.17	
		33	51	9.4	9.8	0.12	
		34	54	9.6	10.3	0.09	
		35	55	10.4	—	0.10	
		36	55	8.8	10.1	0.11	
		37	57	7.6	8.2	0.10	
		38	63	7.8	8.0	0.08	
		39	63	—	6.3	0.14	
		40	66	11.4	11.7	0.15	
		41	76	7.0	7.4	0.05	
	Men	42	33	—	15.1	0.74	0.32
		43	37	7.4	8.9	0.35	
		44	38	9.6	12.0	0.36	
		45	48	8.8	13.7	0.24	
		46	52	10.6	13.6	0.47	
		47	53	14.6	15.0	0.31	
		48	56	—	9.1	0.32	
		49	56	8.4	11.1	0.19	
		50	58	—	7.2	0.16	
		51	60	11.8	14.3	0.19	
		52	62	—	8.5	0.16	

* Expressed in terms of dehydroepiandrosterone equivalent to the formed Zimmermann chromogens.

Gibson and Norymberski, 1954) and/or of "total 17-hydroxycorticosteroids" (17-OH CS: Appleby and others, 1954; 1955).

The results of the assays are presented in the Table. The following points merit emphasis:

Within both groups of subjects the daily excretion of 21-deoxyketols was higher in men than in women: normal men excreted 0.13-0.46 mg. (mean 0.26), normal women 0.03-0.32 mg. (mean 0.14); rheumatoid arthritic men excreted 0.16-0.74 mg. (mean 0.32), rheumatoid arthritic women 0.05-0.31 mg. (mean 0.15).

Within each of the four sub-groups there appears to exist a tendency towards lower excretion levels with

increasing age. This trend is, however, not so pronounced as to vitiate a comparison between the normal group (average age 36 yrs) and the rheumatoid arthritic group (average age 51 yrs). Only one individual (No. 42) of the latter group had a level of 21-deoxyketols significantly above the normal range; this patient was also the only one whose disease was in its early acute phase. All the other rheumatoid arthritic patients excreted normal amounts of 21-deoxyketols, and the average excretion for the whole group closely approached the normal average.

Though the group of subjects investigated was comparatively small, the results seem definite enough

to allow the conclusion that, in rheumatoid arthritis, or at least in its chronic phase, no grossly abnormal excretion of urinary 21-deoxyketols occurs. The small quantities of urinary 21-deoxyketols found in rheumatoid arthritis circumscribe the excretion levels of 17- α -hydroxypregnanolone (I) and hence the isolation of a comparatively large quantity (1.5 mg./day) of (I) reported by Dobriner and others (1951) in one case of rheumatoid arthritis cannot be considered to represent an abnormality generally associated with the disease.

Discussion

A survey of published relevant data reveals that the average excretion of 17-ketosteroids in rheumatoid arthritis is considerably lower than in normal health (Davison and others, 1947; Desmarais, 1949; Wolfson, 1949; Hench and others, 1950; Devis, 1951; Marti, 1951; Venning and others, 1951; Copeman and others, 1952; Kellie and Wade, 1953; Birke, 1954). Similarly low levels of 17-ketosteroids are, however, found in other chronic diseases (Forbes and others, 1947). Devis (1951) carried out a differential analysis of urinary 17-ketosteroids and observed in ten out of fifteen cases of rheumatoid arthritis a decrease in the percentual content of 11-deoxy-17-ketosteroids. Kellie and Wade (1953) found increased ratios of aetiocholanolone to androsterone in three rheumatoid arthritic patients, but pointed out that Robinson and Goulden (1949) observed a similar trend in cases of prostatic cancer. Birke (1954) found normal excretion patterns of individual 17-ketosteroids in 35 patients with rheumatoid arthritis. The urinary corticosteroid levels reported for the disease are difficult to interpret since different assay techniques were employed (Devis and Lemmens, 1950; Hench and others, 1950; Staub and others, 1950; Conestabile and Volpicelli, 1951; Venning and others, 1951; Copeman and others, 1952). Our own initial figures for 17-ketogenic steroids in rheumatoid arthritis were on the average 40 per cent. below normal values (Norymberski and others, 1953); figures now available for a larger number of patients still show a tendency towards lower values, but the average deviation from normal has decreased to approximately 20 per cent. The blood levels of corticosteroids in rheumatoid arthritis were found to be within normal limits (Nelson and others, 1951).

In our interpretation, the work cited above does not lend support to the view that rheumatoid arthritis is associated with a specific defect in steroid metabolism. Moreover, the detection of 17- α -hydroxypregnanolone (I) in normal urine (Dobriner

and others, 1954), together with the evidence here presented, clearly show that, contrary to earlier indications (Dobriner, 1951; Dobriner and others, 1951), an abnormal excretion of (I) has not been demonstrated in rheumatoid arthritis. We wish to emphasize that present knowledge of the steroid excretion pattern in rheumatoid arthritis, or for that matter in any other condition, is only fragmentary, and hence that the conclusions here reached cannot be construed as arguments against a hypothetical causal relation between a derangement of steroid metabolism, or, in particular, between a defect in the adrenocortical function and rheumatoid arthritis.

Summary

The urinary excretion of 17-hydroxy-20-oxosteroids unsubstituted at C₂₁ was studied in 26 healthy persons and in 26 rheumatoid arthritic patients. In the analytical test applied, no difference was found between the two groups of subjects. The significance of this finding is discussed in relation to previous reports of an abnormal excretion of 17- α -hydroxypregnanolone in rheumatoid arthritis. It was concluded that the methods so far employed for the study of steroid excretion in rheumatoid arthritis have failed to reveal a specific metabolic defect.

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Excrétion urinaire des 17-hydroxy-20-oxostéroïdes normale et dans l'arthrite rhumatismale

RÉSUMÉ

On étudia l'excrétion urinaire des 17-hydroxy-20-oxostéroïdes insubstitués en position C_{21} chez 26 sujets normaux et 26 rhumatisants arthritiques. L'épreuve analytique ne montra pas de différence entre les deux groupes. On discute la signification de ce résultat à la

lumière des rapports antérieurs sur l'excrétion anormale de la 17-alpha-hydroxypregnénolone dans l'arthrite rhumatismale. On conclut que les méthodes employées jusqu'à présent pour étudier l'excrétion stéroïde dans l'arthrite rhumatismale ont failli de décèler un défaut métabolique spécifique.

Excreción urinaria de 17-hidroxi-20-oxoesteroides normal y en la artritis reumatoide

SUMARIO

Se estudió la excreción urinaria de 17-hidroxi-20-oxoesteroides insubstituidos en posición C_{21} en 26 sujetos normales y en 26 enfermos con artritis reumatoide. Un examen analítico no mostró diferencia entre los dos grupos. Se discute el significado de este resultado a la luz de los relatos anteriores sobre la excreción anormal de la 17-alfa-hidroxipregnenolona en la artritis reumatoide. Se concluye que los métodos empleados hasta ahora para estudiar la excreción esteroide en la artritis reumatoide han faltado de revelar un defecto metabólico específico.