THE NEUTRAL 17-KETOSTEROIDS IN RHEUMATOID ARTHRITIS AND SPONDYLITIS

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Sjövall (1944), studying the excretion of follicle-stimulating hormone, found that 21 per cent. of female patients under the age of 40 years suffering from rheumatoid arthritis showed evidence of pituitary-ovarian dysfunction.

Davison and others (1947) found no significant alteration in the excretion of 17-ketosteroids in eleven female patients with rheumatoid arthritis, but reported an increased excretion in thirteen male cases of ankylosing spondylitis. In a more recent paper the same authors (1949), dealing with thirty-one male and four female patients suffering from ankylosing spondylitis, found that the high values obtained continued for long periods of time and approached lower levels only when the patients reached a state of exhaustion. Deep x-ray therapy seemed to provide a stimulus for increased excretion, followed by a relative decrease although the symptoms and signs of the disease had abated. Patients showing low activity and slow progress of the disease gave normal figures, whereas those with much activity showed increased levels. Most clinical observations suggest that the adrenals are the principal source of urinary 17-ketosteroids. In the male about one third of the total excreted is also derived from the testes (Fraser and others, 1941).

Very few studies of the estimation of the neutral 17-ketosteroids in rheumatoid arthritis have been made, and the work reported here was begun in 1947 as no previous reports could be found in the literature. However, before it was decided to publish this paper the work of Davison and others (1947; 1949) appeared, and in view of the similarity of the results obtained in rheumatoid arthritis it was thought worth while to present it.

The work of Selye (1946) has opened a new field in the understanding of the role played by the adrenals in disease.

In any chronic condition which may or may not have started acutely, the adrenals, after passing through a stage of over-activity, become exhausted,

with subsequent reduced excretion of the 17-ketosteroids. Advancing years, the long duration of the disease, and any anaemia present, apart from other conditions such as hypothyroidism, Addison's disease, and hypopituitarism, also tend to diminish the excretion of the steroids in the urine (Fraser and others, 1941). In rheumatoid arthritis, which is now recognized as a systemic disease affecting the mesodermal tissues, it is conceivable that the panarthritis and granulomata described by various authors* in the supporting tissues of muscles, nerves, and synovia may also involve the suprarenals, thus interfering further with their normal functions. The factors governing the excretion of 17-ketosteroids in the urine are multiple, and it was obvious that their isolated estimations would be of value only if correlated with factors which are known to be constant in the diseases under study. In this work an attempt was therefore made to correlate the urinary excretion of the 17-ketosteroids with the age and sex of the patient (Hamburger, 1948), the duration of the disease, the sedimentation rate, and the activity of the disease, using for the last factor an arbitrary scale of 0-8 as an "activity index" by rating the degree of loss of weight, intensity of joint pains, sedimentation rate, and anaemia on a three-point scale (0, 1, and 2 points) for each factor. The activity index thus ranged between a minimum of 0 to a maximum of 8 points.

Material

The total urinary neutral 17-ketosteroids were estimated in 87 patients at the Royal National Hospital for Rheumatic Diseases, Bath. The cases were taken at random and consisted of thirty-six female patients and thirty-one male patients suffering from rheumatoid arthritis. In addition eight cases of ankylosing spondylitis, of which two were females, three cases of Still's disease, and nine other cases

* Curtis and Pollard, 1940; Freund and others, 1942, 1945; Steiner and others, 1946; Gibson and others, 1946; Desmarais and others, 1948.

consisting of fibrositis, gout, and non-specific infective arthritis were also included in the series.

The ages of the female patients with rheumatoid arthritis ranged from 21 to 60 years. The duration of the disease was from six months to 27 years. The activity index varied between 2 and 8. In the thirty-one male patients with rheumatoid arthritis the ages ranged from 23 to 67 years. The duration of the disease was from six months to 27 years, and the activity index varied between 1 and 7. The ages of the six male cases of spondylitis ankylopoietica ranged from 21 to 46 years. The disease had lasted from three to ten years, and the activity index varied between 1 and 8. The two cases of ankylosing spondylitis in the females were 41 and 46 years old. The duration of the disease was six years for both, and the activity indices were respectively 7 and 1.

All the cases of spondylitis had received in the past one or several courses of deep x-ray therapy with good results.

The three cases of Still's Disease were 16, 15, and 21 years old, with a duration of 4, 1, and 11 years respectively. Their activity indices were 7, 4, and 6 respectively.

The other cases consisted of seven men and two women. Their ages ranged from 18 to 60 years. The duration was from one to three years and the activity index varied between 0 and 5.

Methods

The determination of the neutral 17-ketosteroids was done by the combined hydrolysis and extraction method of Callow and others (1939) with minor modifications of the technique. The calorimetric estimations were carried out according to Callow (1938) and Zimmermann's (1935; 1936) method, and the colour read in a Spekker photoelectric absorptiometer using an Ilford green filter. The readings were compared with a standard solution prepared from pure crystalline dihydroandrosterone. Blanks were done using absolute alcohol in place of the alcoholic solution. The total neutral 17-ketosteroids was then calculated for 24 hours volume of urine.

Normal values for adult women were taken as 5 to 15 mg. per 24 hours, with a mean of 9 mg. per 24 hours, and normal values for adult males were taken as 8 to 23 mg. per 24 hours with a mean value of 14 mg. per 24 hours. The sedimentation rate and haematocrit estimations were by the method of Collins and others (1939). The corrected suspension stability (C.S.S.) is the percentage volume of red cells after one hour, corrected for any anaemia present, taking a haematocrit reading of 42 per cent. as being normal. A corrected suspension stability of 85 per cent. or more is taken as normal, and a reading below 60 per cent. is considered maximal.

Results

In the thirty-six female patients suffering from rheumatoid arthritis the level of 17-ketosteroids ranged from 1.9 to 21.8 mg. in 24 hours with a mean value of 8.6 mg. Twenty-seven (75 per

cent.) of cases fell within the normal range of 5 to 15 mg. in 24 hours. Two cases gave low normal values of respectively 4 mg. and 4.1 mg. Four cases with low values ranging from 1.9 to 3.2 mg. fell within the older age group, with an average age of 49 years. It is interesting to note that they had all reached the menopause. Two cases showed high normal values of 17 and 17.3 mg. One case with a level of 21.8 mg. was 31 years old, with an activity index of 7.

In the thirty-one male patients with rheumatoid arthritis the 17-ketosteroids ranged from 3.7 mg. to 27.4 mg. for 24 hours with a mean value of 12 mg. Twenty-four (77.4 per cent.) cases fell within the normal range of 8 to 23 mg. per 24 hours. Two cases gave low normal values of 6.1 and 6.2 mg. per 24 hours. Four cases with low values ranging from 3.7 to 4.7 mg. fell in the old-age group with an average age of 54.7 years. Only one case, of a boy aged 23 years with an activity index of 2, gave a moderately high value of 27.4 mg.

In the six male cases of ankylosing spondylitis the 17-ketosteroids ranged from 8.4 to 13.2 mg. per 24 hours, with a mean value of 10.2 mg. The two female cases gave values of 6 mg. and 13.6 mg. respectively. The three cases of Still's disease gave values of 8.2 mg., 6.0 mg., and 5.9 mg. respectively.

The other nine miscellaneous cases gave values ranging from 5.7 mg. to 23.2 mg., with a mean value of 13.7 mg. per 24 hours.

Correlation coefficients were calculated between the level of 17-ketosteroids and the age of the patient, the duration of the disease, the haematocrit, the corrected suspension stability, and the activity index, both in male and female patients suffering from rheumatoid arthritis. In the female patients the correlation coefficients at 5 per cent. level of significance, ≈ 0.33 for 36 pairs, indicated a significant correlation of -0.382 between the age of the patients and the 17-ketosteroids. The other factors gave no significant correlations. In the males the correlation coefficient at 5 per cent. level of significance, ≈ 0.355 for 31 pairs, indicated a significant correlation of -0.435 between the 17-ketosteroids and the age of the patient and also a significant correlation of -0.435 between the 17-ketosteroids and the activity index. The other factors gave no significant correlation. None of the above were significant at 1 per cent. level. No attempt at calculating a multiple or a partial correlation coefficient has been made.

Discussion

The excretion of the 17-ketosteroids in rheumatoid arthritis was found to fall within normal limits

in 76.1 per cent. of all cases. The significant correlation between the age of the patients and the 17-ketosteroids in both male and female patients is also true for normal individuals. No satisfactory explanation could be found for the lack of correlation in the female cases between the 17-ketosteroids and activity index and the presence of a significant correlation in the males between these factors.

The eight cases of ankylosing spondylitis had all received one or several courses of deep x-ray therapy before the estimations were done. Comparing the results obtained with the findings of Davison and others (1947; 1949), mean values of 10.2 for males and values of 6 mg. and 13.6 mg. for the two female cases are low.

The values found for the three cases of Still's disease fell within normal range for the ages of the patients. The other nine miscellaneous cases gave values which were within the normal range, with a mean value of 13.7 mg.

From the above findings the estimation of 17-ketosteroids in rheumatoid arthritis is found to be of very little clinical value. If the urinary excretion of 17-ketosteroids is taken as a reflection of the androgenic function of the adrenals, we find that this factor is not materially affected in this disease. It would, however, be of interest to study the excretion of glyconic corticoids in parallel with the excretion of 17-ketosteroids, which would give a more detailed picture of the activity of two different aspects of adrenal function in the same patient.

Summary

The excretion of neutral urinary 17-ketosteroids in eighty-seven cases of rheumatic conditions were estimated by the Callow-Zimmermann method. In thirty-six female and thirty-one male patients suffering from rheumatoid arthritis, 75 per cent. and 77.4 per cent. of cases respectively, fell within normal limits of excretion. A significant correlation was found between the 17-ketosteroids and the age of the patients, both in male and female cases. In the males a significant correlation was also found between the activity index and the 17-ketosteroids, but none in the female patients. No explanation for this discrepancy could be put forward. From these findings the estimation of 17-ketosteroids in rheumatoid arthritis was found to be of little clinical value.

The mean value for eight cases of ankylosing spondylitis was found to be low when compared with the findings of Davison and others (1947; 1949). All the cases had received deep x-ray therapy. Nine other miscellaneous cases, and three cases of Still's disease, were all within normal limits.

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Les 17-Cétostéroïdes neutres dans l'Arthrite Rhumatismale et la Spondylite.

RÉSUMÉ

L'excrétion urinaire des 17-cétostéroïdes neutres fut déterminée dans 87 cas d'affection rhumatismale par la méthode de Callow-Zimmermann. Chez 36 femmes et 31 hommes atteints d'arthrite rhumatismale cette excrétion se trouvait endéans les limites normales dans 75 pour cent et 77.4 pour cent de cas respectivement. On a trouvé un rapport significatif, chez les hommes et chez les femmes, entre les 17-cétostéroïdes et l'âge des malades. De même, on a observé un rapport significatif entre l'indice d'activité et les 17-cétostéroïdes chez les hommes, mais pas chez les femmes.

On a trouvé que le chiffre moyen, par rapport aux résultats obtenus par Davison et coll. était bas dans huit cas de spondylite ankylosante. Tous les cas furent traités par des rayons x profonds. Dans neuf cas divers et dans trois cas de maladie de Still les chiffres se trouvaient endéans les limites normales.