A COMPARISON OF URINARY OESTROGEN LEVELS IN NORMAL MALE SOUTH AFRICAN BANTU AND EUROPEAN SUBJECTS

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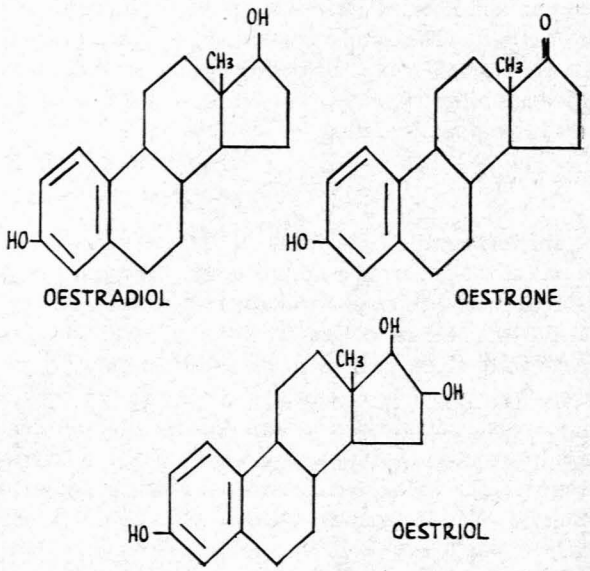
In the South African Bantu, the frequency of biochemical dysfunction of the liver is well known, being present in over two-thirds of adults examined, the great majority of whom show no clinical symptoms.[1-2] Further, hepatic cirrhosis is present in about 10% of adults examined at necropsy, while hepatic fibrosis and primary carcinoma of the liver are much more prevalent in the Bantu than in the European population.[3-8]

The liver exerts an important influence on hormonal metabolism in maintaining the delicate balance between oestrogens and androgens. In chronic liver disease, disturbance of sex hormone balance is frequently encountered. Thus, menstrual disturbances frequently occur in the African female and gynaecomastia, testicular atrophy, loss of pectoral and axillary hair, loss of libido, and impotence, are commoner in African than in European males.[9] Gillman and Gillman[10] have alluded to the correlation between gynaecomastia and testicular atrophy on the one hand and liver damage, on the other. These authors, however, state that they were unable to correlate the presence or absence of gynaecomastia with the extent or severity of the pathologic changes in the liver. Davies[11] suggested that the different incidence of a number of pathological states in the African from that found in European subjects might be due in the first instance to the high incidence of liver disease caused by malnutrition, and then that, as a result of the hepatic dysfunction, the Africans are subjected to wholesale oestrinization from an early age.

The liver plays a dominant role in normal individuals in the intermediate metabolism of oestrogens. This view is supported by observations on laboratory animals, human subjects and by *in vitro* experiments.[12-17]

Experiments on normal male subjects indicate that after intramuscular injections of large doses of oestrogens so much of the hormone is lost in the process of intermediate metabolism that only relatively small quantities are recovered from the urine. This major loss of oestrogenic activity is variously described as being due to destruction, inactivation or conversion of the hormone by the liver.[16] Thus, injected oestrogens, in the presence of a normally functioning liver, lose much of their activity but, in the presence of liver disease, high concentrations of oestrogen are recovered. The greater the degree of liver damage, the greater is the failure to inactivate or convert endogenous, as well as exogenous, oestrogens.[16]

The oestrogenic steroids are oestradiol, oestrone and oestriol. The oestradiol fraction may be regarded as the true oestrogenic hormone and the oestrone and oestriol fractions as breakdown products. Oestrone is an intermediary product in the transformation of oestradiol to oestriol. Schiller and Pincus[18-19] have shown that oestradiol and oestrone are interconvertible, and that both these steriods can be excreted as oestriol. Alpha oestradiol is approximately 12 times more potent than oestrone and at least 80 times more potent than oestriol. These wide differences in biological activity depend upon comparatively slight variations in chemical structure:



Until quite recently, reliable methods for the determination of urinary oestrogens were mainly confined to biological assays. In 1955 J. B. Brown[20] described a technique for the chemical estimation of urinary oestrogens. Marrian[20] in discussing this method, referred to it as being workable and convenient and accurate enough to determineas little as 5 μg. each of oestradiol, oestrone and oestriol in a 24-hour specimen of urine.

In view of the high incidence of liver disease in the South African Bantu and the important role played by the liver in steroid metabolism, we decided to investigate urinary oestrogen levels in normal Bantu male subjects and to compare our findings with those found in a similar group of normal European male subjects.

Material and Method

We obtained 24-hour specimens of urine from 21 European male subjects, who were members of the staff of this Institute and in excellent health, and from 21 Bantu male subjects. Of the latter, 15 were employed at this Institute and were in excellent health and 6 were patients suffering from minor surgical injuries but assessed clinically as normal and healthy. The age ranges and mean ages for the European

groups were 20—48 years (mean 30·5) and for the Bantu group 20—45 years (mean 31) years respectively.

The technique we used for estimating total oestrogen, oestradiol, oestrone and oestriol was that described by Brown.[20]

RESULTS

Tables I and II show the amounts of total oestrogen, and the absolute and relative amounts of the 3 fractions oestradiol, oestrone and oestriol, which we found in 24-hour specimens of urine from normal Bantu and European male subjects.

TABLE I. ANALYSIS OF THE OESTROGEN CONTENT OF 24-HOUR SPECIMENS OF URINE IN NORMAL BANTU MALE SUBJECTS

Total Oestrogen (μg.)	*Oestradiol* (μg.)	*Oestradiol* %	*Oestrone* (μg.)	*Oestrone* %	*Oestriol* (μg.)	*Oestriol* %
13·3	3·9	29·3	5·5	41·4	3·9	29·3
9·1	0·0	0·0	5·5	60·4	3·6	39·6
12·4	3·2	25·8	3·7	29·8	5·5	44·4
21·0	6·4	30·5	9·7	46·2	4·9	23·3
8·3	3·1	37·3	3·0	36·1	2·2	26·6
12·3	2·5	20·3	7·9	64·2	1·9	15·5
10·6	1·8	17·0	2·4	22·6	6·4	60·4
8·8	1·4	15·9	3·4	38·6	4·0	45·5
11·6	4·6	40·0	6·2	53·4	0·8	6·6
6·6	0·4	6·0	3·0	45·5	3·2	48·5
10·9	3·4	31·2	5·5	50·5	2·0	18·3
11·2	1·3	11·6	5·5	49·1	4·4	39·3
18·2	4·7	25·8	11·3	62·0	2·2	12·2
18·9	4·0	21·2	10·4	55·0	4·5	23·8
5·0	1·1	22·0	2·3	46·0	1·6	32·0
10·7	1·8	16·8	3·4	31·8	5·5	51·4
8·5	0·0	0·0	5·4	63·5	3·1	36·5
10·9	1·7	15·6	6·4	58·7	2·8	25·7
17·3	5·3	30·6	7·3	42·2	4·7	27·2
5·2	0·9	17·3	2·0	38·5	2·3	44·2
9·2	1·2	13·0	5·0	54·4	3·0	32·6
MEAN VALUES 21 SUBJECTS						
11·5	2·5	21·8	5·5	47·8	3·5	30·4

TABLE II. ANALYSIS OF THE OESTROGEN CONTENT OF 24-HOUR SPECIMENS OF URINE IN NORMAL EUROPEAN MALE SUBJECTS

Total Oestrogen (μg.)	*Oestradiol* (μg.)	*Oestradiol* %	*Oestrone* (μg.)	*Oestrone* %	*Oestriol* (μg.)	*Oestriol* %
4·4	1·1	25·0	2·7	61·3	0·6	13·7
13·1	2·2	16·8	3·8	29·0	7·1	54·2
6·1	2·9	47·5	2·0	32·7	1·2	19·7
10·9	0·7	6·4	9·8	89·9	0·4	3·7
7·2	0·8	11·1	4·4	61·1	2·0	27·8
7·6	0·9	11·8	3·4	44·7	3·3	43·5
4·7	0·0	0·0	3·0	63·8	1·7	36·2
5·7	0·0	0·0	3·6	63·2	2·1	36·8
4·6	0·7	15·2	2·5	54·3	1·4	30·5
13·7	0·9	6·6	2·9	21·2	9·9	72·2
4·6	1·1	23·9	1·7	36·9	1·8	39·2
7·3	1·8	24·6	3·7	50·7	1·8	24·7
10·2	1·2	11·8	7·4	72·5	1·6	15·7
9·7	0·6	6·2	6·3	64·9	2·8	28·9
3·8	0·2	5·3	2·9	76·3	0·7	18·4
8·7	2·0	23·0	4·7	54·0	2·0	23·0
15·4	3·1	20·1	9·0	58·4	3·3	21·5
6·5	0·4	6·2	3·6	55·4	2·5	38·4
9·9	1·9	19·2	6·7	67·6	1·3	13·2
9·2	1·0	10·9	4·1	44·6	4·1	44·5
8·3	0·0	0·0	4·1	49·4	4·2	50·6
MEAN VALUES 21 SUBJECTS						
8·0	1·1	13·9	4·3	53·7	2·6	32·4

The mean total urinary oestrogen value in the non-European was 11·5 μg. as compared with 8·0 μg. in the European.

The mean oestradiol value was 2·5 μg. in the non-European as compared with a mean value of 1·1 μg. in the European; whilst the percentages of oestradiol to total oestrogen were 21·8% and 13·9% respectively.

The mean oestrone value was 5·5 μg. with a percentage of 47·8 in the non-European as against 4·3 μg. and 53·7% in the European.

The mean oestriol value was 3·5 μg. and 30·4% in the non-European and 2·6 μg. and 32·4% in the European.

These results when subjected to statistical analysis show the following:

1. A very highly significant increase in the total oestrogen level per 24-hour specimen of urine in the non-European when compared with the European ($p = < 0{\cdot}005$).

2. A very highly significant increase in the absolute oestradiol level ($p = < 0{\cdot}005$) and a statistically significant increased percentage of oestradiol in the non-European ($0{\cdot}01 < p < 0{\cdot}025$).

3. No significant differences either in the absolute or relative amounts in the oestrone and oestriol fractions in the two racial groups.

DISCUSSION

Our results show, that even in the apparently 'healthy' South African male Bantu a significantly different oestrogenic pattern exists from that in the European counterpart. Thus, the Bantu shows a significant increase in total urinary oestrogen levels, as well as in the very active and potent oestradiol fraction. Our findings, when taken in conjunction with the available evidence of increased oestrogen levels in patients suffering from liver disease, further substantiates the known high incidence of liver impairment or dysfunction in the so-called 'normal' Bantu.

We have merely investigated urinary oestrogen levels, but available evidence exists that there is a multiglandular endocrine disbalance in liver disease, and one would probably find evidence in the normal Bantu of adrenal overactivity resulting in secondary pituitary depression leading to lowered urinary gonadotrophin levels.

Lloyd and Williams[21] suggest that the liver participates in steroid metabolism by aiding the interconversion of oestradiol and oestrone to oestriol, by the formation of inactive oxidative products from oestrogen, and in the conjugation of oestrogens for inactivation and excretion. They postulate that in liver disease there is a diminution in the release of follicle-stimulating hormone, a suppression of spermatogenesis and follicle maturation, and oestrogenic stimulation of target organs. Owing to the decrease in the inactive oxidative products there is a decreased release of the pituitary luteinizing hormone and adrenotrophin leading to menstrual disturbances, loss of axillary hair and diminished urinary 17-ketosteroid excretion.

The 'disease pattern' of the Bantu differs markedly from that of the European. Among the former, for instance, there is a high incidence of certain deficiency diseases, a high incidence of liver disease, especially primary carcinoma, and a low incidence of atherosclerosis, diabetes, gall-stones, peptic ulcer and certain forms of cancer.[22] Is it not possible that the altered pattern of disease in the Bantu is due to the marked hormonal and endocrine disturbances found in this racial group?

Davies[11] suggests that the functional capacity of the liver is impaired, owing to malnutrition at an early stage in

infancy. Further dietetic privations, especially if accompanied by acute and chronic infections, lead later in life to further hepatic damage. Thus, from an early age, owing to this liver damage, the African may be subject to over-oestrogenization. If this is the case, then general changes should occur in the physique and the disease pattern of the African should be profoundly altered. Evidence of feminization, gynaecomastia and alterations in the general body configuration should be evident. The endocrine glands would be affected and the incidence of certain endocrine disorders should be altered. This, in effect, is what Davies observed in Uganda.

So far as primary carcinoma of the liver is concerned, the known carcinogenic properties of oestrogens should lead in the African to a high incidence of carcinoma of the liver and, since oestrogenization occurs from an early age, then the age incidence of this type of cancer should be lower than the usual 'cancer age'. This in fact is what happens in the African.

A striking feature of the disease pattern in the Bantu is the low incidence of coronary atherosclerosis and low serum-cholesterol levels. Cannot this low incidence also be correlated with the high oestrogen levels in the Bantu? Eilert[23] has shown that increased oestrogen levels depress serum-cholesterol; and Boyle[24] has reported reduction in all serum lipids, including cholesterol, during long-term administration of oestrogens. Thus, alterations in the balance between male and female sex hormones arising from liver dysfunction may well be involved in the observed differences between cholesterol levels in African and European subjects and in the low incidence of atherosclerosis in the former.

The high incidence of liver disease and dysfunction in the South African Bantu is considered by many to be largely the result of malnutrition. Incidentally, loss of libido, gynaecomastia and testicular atrophy were also noted in the severe malnutrition of prisoners of war.[25] The different pattern of disease in the Bantu could thus be intimately connected with malnutrition and kwashiorkor in the African infant, and later in life repeated episodes of undernutrition, especially if accompanied by infection, lead to permanent liver damage. The frequency of certain diseases and the rarity of others could thus be due indirectly to nutritional changes in infancy which lead to hormonal imbalance in later life.

SUMMARY

1. Urinary oestrogen levels were determined in 21 normal male European and 21 normal male Bantu subjects.

2. Highly significant increases in the total oestrogen level and in the oestradiol fraction were found in the Bantu group.

3. An attempt is made to correlate the 'disease pattern in the Bantu' with liver dysfunction resulting in endocrine imbalance.

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