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# SUMÁRIO

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# DERMATOGLYPHIC STUDIES IN TURNER'S SYNDROME

J.C. CABRAL DE ALMEIDA (*), H. KAYTH (**), M. A. BARCINSKI (**), J. NAYA (**), M.C. ABREU (**), R.S. MELLO (**) J. SANTOS (**), M.H. CARDOSO (**), J. RODRIGUES (***).

The main dermatoglyphic features of Turner's syndrome were initially pointed out by Penrose & Polani and the posterior works of Almeida et al ([2])., Uchida et al ([3]), Almeida et al ([4])., Forbes Holt et al ([6])., Penrose ([7]) confirmed them.

This paper presents the final result of the dermatoglyphic investigations proceeded in 25 patients with fermale Gonadal Dysgenesis (Turner's Syndrome and Allied Conditions) studied at the Laboratório de Citogenética Humana do Instituto de Biofisica e 3ª Cadeira de Clínica Médica da Universidade Federal do Rio de Janeiro.

MATERIAL:

Table I summarizes the main cytogenetic and clinical features of the cases. All the cases presented short, stature, clinical

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and laboratorial evdences of primary hypogonadism associated to congenital defects. The few patients below the age of normal puberal development onset were referred to us because of short stature, multiple stigmata plus either or both: webbing of the neck and coarctation of the aorta.

TABLE I

SUMMARY OF THE CYTOGENETIC AND CLINICAL FINDINGS OF THE TURNER'S SYNDROME PATIENTS STUDIED

| | CASE | CHROMOSOME PATTERN | NUCLEAR SEXING | AGE | MAIN CLINICAL FEATURES |
|---|---|---|---|---|---|
| 1 | FI | XO | - | 10 m | Webbing of the neck + congenital lymphoedema |
| 2 | EM | XO | - | 21 m | Webbing of the neck + congenital lymphoedema + somatic stigmata |
| 3 | MIG | XO | - | 11 y | Webbing of the neck + congenital lymphoedema + aorta coarctation |
| 4 | LE | XO | - | 13 y | Short stature + short neck + no secondary sexual characteristics |
| 5 | SR | XO | - | 14 y | Short stature + short neck + somatic stigmata + no puberal development |
| 6 | AM | XO | - | 17 y | Short stature + primary amenorrhea + no puberal development + colour blindness |
| 7 | MB | XO | - | 17 y | Webbing of the neck + short stature + primary amenorrhea + no puberal development |
| 8 | ER | XO | - | 17 y | Short stature + primary amenorrhea + no puberal development |
| 9 | CG | XO | - | 20 y | Short stature + primary amenorrhea + no puberal development |
| 10 | ZF | XO | - | 24 y | Short stature + primary amenorrhea + no puberal development |
| 11 | MBA | XO | - | 26 y | Short stature + primary amenorrhea + no puberal development |
| 12 | OF | XO | - | 22 y | Short Stature + primary amenorrhea + no puberal development |
| 13 | MLAC | XO | - | 15 y | Short stature + webbing of the neck + somatic stigmata + no puberal development |
| 14 | JDP | XO | - | 19 y | Short stature + short neck + no puberal development + primary amenorrhea |
| 15 | MTA | XO | - | 15 y | Short stature + no puberal development + primary amenorrhea |
| 16 | MJM | XO | - | 14 y | Short stature + short neck + no puberal development + colour blindness |
| 17 | CR | XO/XX | +2% | 20 y | Short stature + short neck + no puberal development + colour blindness |
| 18 | CLS | XO/XX | + | 21 y | Short stature + primary amenorrhea + no puberal development |
| 19 | MES | XO/XX | + | 18 y | Short stature + moderate webbing of the neck + spontaneous menses + aorta coarctation |
| 20 | CV# | XO/XX/XXX | +/++3% | 18 y | Short stature + primary amenorrhea + no puberal development + aorta coarctation |
| 21 | EMD | XO/Xf | - | 15 y | Short stature + primary amenorrhea + no puberal development |
| 22 | CD | XO/XX/Xf/XXi | +12% | 21 y | Short stature + primary amenorrhea + no puberal development |
| 23 | VM | XXd | +(small body) | 18 y | Short stature + primary amenorrhea + no puberal development |
| 24 | LBS | Xi | + | 24 y | Short stature + primary amenorrhea + no puberal development + mentally retarded |
| 25 | MD | XO/XY | - | 17 y | Short stature + short neck + no puberal development + hypertrophy of the clitoris + primary amenorrhea + artificially induced menses. Laparotomy : uterus + "rudimentary gonads" + fallopian tubes. Histology : undifferentiated stroma + clumps of Leydig cells. Bilateral fallopian tubes. Tubular structures similar to epididymus. |

f = fragment
i = isochromosome
d = deletion
- = negative
+ = positive

Chromosome studies were performed in all cases and were obtained through peripheral blood culture. Only cases 8, 11 and 25 had also bone-marrow chromosome studies performed. As only blood was studied mosaicism could not be ruled out in the XO considered cases.

Both male and female control groups were composed of 50 mem and 50 women with normal stature and no evidences of hypogonadism, sellected among medical students and University personnel.

Partial result of 17 of this present series cases were presented by Almeida et al(4). at the VII Congresso Brasileiro de Endocrinologia e Metabologia em 1966.

Finger-print analysis were made in 19 patients and palm-print analysis in all 25 cases.

Both 50 males and 50 females composing the control groups had their finger-prints and palm-prints analysed.

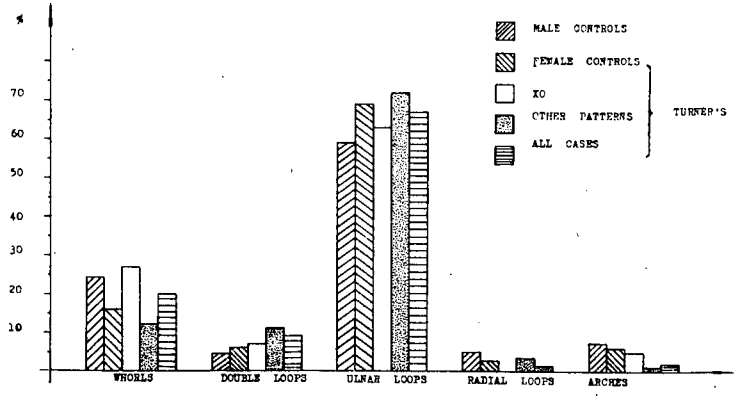
## RESULTS:

### 1 — FINGER PRINT STUDIES

An increase in the total finger ridge-counts in Turner's syndrome, has been uniformely found by different authors.

Penrose ([8]), recently, has suggested a relationship between the total finger ridge-count and the different sex-chromosome patterns. There would be a related lowering of the total finger ridge-count number in relation to an increase in the sex-chromosomes; in such a way that XO individuals are those who present the largest total finger ridge-count, being followed by normal males, normal females, XXX females, XXY males and more complex sex-chromosome constitutions.

DISTRIBUTION OF DIGITAL PATTERNS IN TURNERùS SYNDROME AND CONTROLS AND FERMALES




The frequency of the different digital patterns in the different groups are shown in Table II together with the mean value of dermal ridge count for each digital pattern (see Table II and Fig. 1).

TABLE II

DISTRIBUTION OF DIGITAL PATTERNS IN TURNER'S SYNDROME AND CONTROLS MALE AND FEMALE.
MEAN VALUES AND STANDARD DEVIATION FOR DERMAL RIDGE COUNT FOR EACH PATTERN.

| GROUPS | CHROMOSOME PATTERN | No OF CASES | WHORL | | | DOUBLE LOOP | | | ULNAR LOOP | | | RADIAL LOOP | | | ARCH | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | % | MEAN AND STANDARD DEVIATION | No | % | MEAN AND STANDARD DEVIATION | No | % | MEAN AND STANDARD DEVIATION | No | % | MEAN AND STANDARD DEVIATION | No | % |
| TURNER'S SYNDROME | XO | 10 | 27 | 27.00 | 20.74 ± 0.63 3.24 | 7 | 7.00 | 22.85 ± 1.9 5.20 | 63 | 63.00 | 16.17 ± 0.76 6.03 | - | - | - | 3 | 3.00 |
| | XO/XX<br>XO/XX/XXX<br>XO/XX[f]<br>XO/XX[f]/XX[i]/XI<br>XX[d]<br>XX[i] and XO/XY | 9 | 11 | 12.22 | 16.18 ± 2.15 7.13 | 10 | 11.11 | 26.30 ± 1.93 6.13 | 65 | 72.22 | 15.30 ± 0.68 5.48 | 3 | 3.33 | 13.00 ± 3.10 5.35 | 1 | 1.11 |
| | ALL CASES | 19 | 38 | 20.00 | 19.42 ± 0.72 4.44 | 17 | 8.95 | 24.88 ± 1.30 5.41 | 128 | 67.36 | 15.73 ± 0.49 5.54 | 3 | 1.57 | 13.00 ± 3.10 5.35 | 4 | 2.10 |
| CONTROLS | NORMAL MALES | 50 | 121 | 24.20 | 17.48 ± 0.47 5.27 | 22 | 4.40 | 15.09 ± 1.30 6.11 | 294 | 58.80 | 12.22 ± 0.50 8.92 | 26 | 5.20 | 11.65 ± 2.29 9.74 | 37 | 7.40 |
| | NORMAL FEMALES | 50 | 80 | 16.00 | 17.48 ± 0.62 5.60 | 31 | 6.20 | 18.64 ± 0.87 4.84 | 343 | 68.60 | 12.33 ± 0.50 9.28 | 13 | 2.60 | 13.15 ± 3.87 13.95 | 28 | 5.60 |

As has been shown by Holt ([6]) in her excellent paper, our findings also indicate a smaller frequency of arches in the Turner's compared to the controls; however, opposed to her findings and the other countries usual population findings our male controls showed more arches than the females. The rare finding of a IV left finger radial loop was seen in 1 Turner and in one female control.

TABLE III

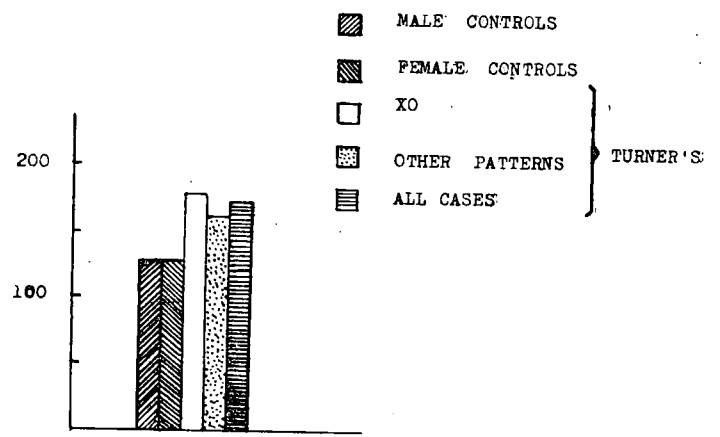
MEANS AND STANDARD DEVIATION FOR TOTAL FINGER RIDGE COUNT IN TURNER'S SYNDROME AND IN CONTROLES MALE AND FEMALE

| GROUPS | CHROMOSOME PATTERN | Nº OF CASES | TOTAL FINGER RIDGE COUNT | |
|---|---|---|---|---|
| TURNER'S SYNDROME | XO | 10 | 173.90 ± 12.85 | 42.80 |
| | XO/XX<br>XO/XX/XXX<br>XO/XX$^{f}$<br>XO/XX$^{f}$/XX$^{i}$/XX<br>XX$^{d}$<br>XX$^{i}$ AND XO/XY | 9 | 163.90 ± 19.35 | 58.1 |
| | ALL CASES | 19 | 169.15 ± 11.5 | 49.4 |
| CONTROL | NORMAL MALES | 50 | 127.20 ± 6.7 | 46.5 |
| | NORMAL FEMALES | 50 | 127.58 ± 6.4 | 45.0 |

Statistical analysis of the mean value of the dermalridge count for each different pattern showed no statistically significant difference only between the Turner's and the female group for whorls and between the Turner's and both controls for radial loops. For all other patterns, including double loops (which we consider as equivalent to whorls), and, obviously excluding arches, the statistical analysis showed the difference of the dermal-ridge count per pattern to be highly significant between the Turner's and the controls ($p < 0.01$). For the

means, standard deviations and statistical conclusion for the total finger ridge-count in Turner's and control groups see Table III and Fig. 2.

MEANS FOR TOTAL RIDGE COUNT IN TURNER'S SYNDROME AND CONTROLS: MALES AND FEMALES




In our series there was an unexpected finding of no difference between the male and female groups. However, the female group showed the same total finger ridge-count as found in other coutries (Penrose[8], Holt et al[6]) our male group showed a much smaller total presenting with the same value as the female controls. If in Penrose's series 825 controls of both sexes were studied in Holt's series, however, who found the same values as Penrose's only 50 females and 39 males were studied as controls. No explanation for our findings seems adequate except that for a more racially mixed population as ours a larger number of controls would be necessary.

But at the same time the racial differences would interfere in both male and female groups once there was no special concentration of negroes in any of the control group. Besides it is known that negroes tend to present more whorls than

arches which would be an aditive value to the total finger ridge-count (9).

The differences of the total finger ridge-count is highly significant between the Turner's and male and female controls as has been found by other authors.

## II. PALM-PRINT STUDIES

The main features examined in the palm-prints collected were:

1) a-b ridge count per hand
2) maximum atd angle value per hand
3) t position measurement per hand
4) frequency of unuscual direction of the *t* line terminating in the second interdigital area and *a* line ending near the base of the thumb, per case.
5) frequency of hypothernar and thenar patterns, per case
6) frequency of the simian crease, per case
7) frequency of fusions of the distal Triradii and of the absence of distal Triradii per case
8) frequency of interdigital true patterns per case.

### 1) *a-b ridge count per hand*

Holt (6) has shown mean values for the sum of both hands of the a-b ridge count in Turner's to be highly significantly different compared to male and female controls. Our result as shown in Table IV showed, the same highly significant difference between the Turner's and the male and female controls.

### 2) *Maximum atd angle per hand*

Penrose (1), Almeida (2), Uchida (3), and Holt (6) have shown a higher value of the maximum atd angle in Turner's syndrome. Our actual findings are summarized in Table IV.

### 3) *t position measurement per hand*

The maximum atd angle can be considered as an indirect measurement of the position of the axial triradius. The t po-

sition measurement gives a more exact idea of the position of the axial triradius; once the factors which may influence the values for atd angle (such as a wider stretching of the distal part of the hand at the moment of printing) do not occur.

Our findings of the t position measurement can be found in Table IV.

TABLE IV

MEANS AND STANDARD DEVIATIONS FOR ab RIDGE COUNT PER HAND, MAXIMUM ATD ANGLE PER HAND AND T POSITION IN TURNER'S SYNDROME AND IN CONTROLS MALE AND FEMALE

| GROUPS | CHROMOSOME PATTERN | Nº OF CASES | ATD | t | ab |
|---|---|---|---|---|---|
| TURNER'S SYNDROME | XO | 16 | 49.75 ± 2.30 13.08 | 21.46 ± 3.00 16.00 | 47.87 ± 0.96 5.46 |
| | XO/XX<br>XO/XX/XXX<br>XO/XX$^{f}$<br>XO/XX$^{f}$/XX$^{i}$/XX<br>XX$^{d}$<br>XX$^{i}$ and XO/XY | 9 | 52.00 ± 3.31 14.05 | 27.46 ± 4.26 12.80 | 46.44 ± 1.71 7.28 |
| | ALL CASES | 25 | 50.56 ± 2.62 13.13 | 23.62 ± 3.3 15.15 | 47.36 ± 0.87 7.07 |
| CONTROLS | NORMAL MALES | 50 | 42.00 ± 1.42 9.95 | 17.78 ± 1.81 12.63 | 41.62 ± 0.62 6.24 |
| | NORMAL FEMALES | 50 | 42.4 ± 0.9 6.20 | 14.00 ± 1.60 11.20 | 42.84 ± 0.75 7.53 |

It is noteworthy that our male controls present a mean value of 17.78% ± 12.68 which according to the conventional classification is to be considered as t' (from 15% to 39.9%). However our Turner's t position measurement is also classified as t' (23.62 ± 15.15) the difference between both normal males t' and Turner's t' are highly significant. The normal different values for t position measurement in males and females is preserved in our series and while the females have a 14.00 ± 11.20 (t) value there is no significant difference between the t value in both controls.

4) *Unsual direction of t and a line per case*

This finding was shown by Holt et al(6) who found it in about 50% (mainly on the left hand) of the Turner's cases compared to 18% of the normal males and 8% of the normal females. Our findings for this item are summarized in Table V and Fig. 3.

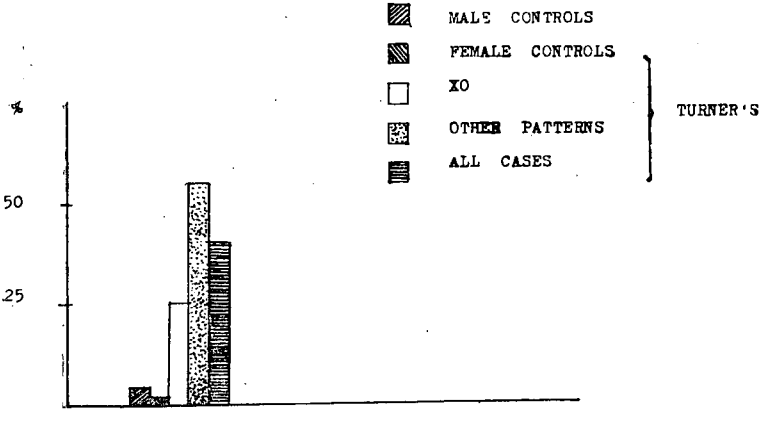
In our experience we are bound to consider this finding as a most important dermatoglyphic aspect due to its much higher frequency in the Turner's cases compared to both controls.

TABLE V

FREQUENCY OF UNUSUAL DIRECTION OF T AND A LINE IN PATIENTS WITH TURNER'S SYNDROME AND IN CONTROL MALES AND FEMALES

| GROUPS | CHROMOSOME PATTERN | Nº OF CASES | LEFT HAND | RIGHT HAND | BOTH HANDS | TOTAL |
|---|---|---|---|---|---|---|
| TURNER'S SYNDROME | XO | 16 | 2 | - | 2 | 4 (25%) |
| | XO/XX, XO/XX/XXX, XO/XX, XO/XX, /XX, XXd XX, XO/XY | 9 | 2 | - | 3 | 5 (55.55%) |
| | ALL CASES | 25 | 4 | - | 5 | 9 (36%) |
| CONTROL | NORMAL MALES | 50 | 1 | - | 1 | 2 (4%) |
| | NORMAL FEMALES | 50 | - | - | 1 | 1 (2%) |

FREQUENCY OF UNUSUAL DIRECTION OF t AND a LINE IN PATIENTS WITH TURNER'S SYNDROME AND IN THE CONTROLS MALE AND FEMALE



5) *Hypothenar and thenar patterns per case.*

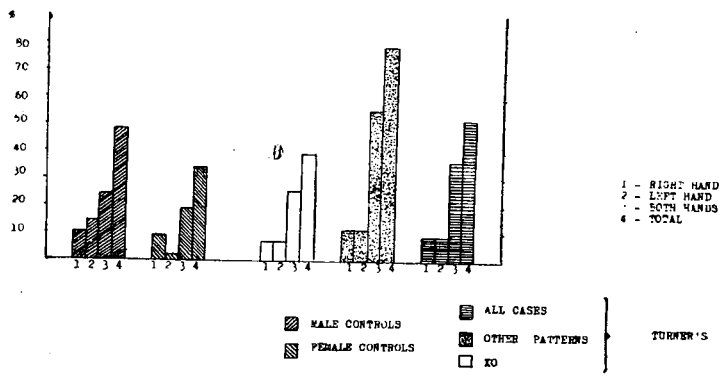
The summary of the frequency of hypothenar pattern in our series is seen in Table VI and Fig. 4. It is principally

T A B L E VI

FREQUENCY OF HYPOTHENAL PATTERNS IN PATIENTS WITH TURNER'S SYNDROME AND IN CONTROLS MALES AND FEMALES

| CHROMOSOME PATTERN | Nº OF CASES | RIGHT HAND | LEFT HAND | BOTH HANDS | TOTAL |
|---|---|---|---|---|---|
| XO | 16 | 1 (6.25%) | 1 (6.25%) | 4 (25.00%) | 6 (37.50%) |
| XO/XX XO/XX/XXX XO/XX$^{f}$ XX$^{i}$ XO/XX$^{f}$/XX$^{i}$/XX XO/XY XX$^{d}$ | 9 | 1 (11.11%) | 1 (11.11%) | 5 (55.55%) | 7 (77.77%) |
| ALL CASES | 25 | 2 (8%) | 2 (8%) | 9 (36.00%) | 13 (52.00%) |
| MALE CONTROLS | 50 | 5 (10%) | 7 (14%) | 12 (24%) | 24 (48%) |
| FEMALE CONTROLS | 50 | 4 (8%) | 1 (2%) | 12 (24%) | 17 (34%) |

FREQUENCY OF HYPOTHENAR PATTERN IN TURNER'S SYNDROME AND IN CONTROLS MALES AND FEMALES




DISTRIBUTION OF DIGITAL PATTERNS IN TURNER'S SYNDROME AND CONTROLS MALES AND FEMALES

common the presence of large hypothenar patterns as has been shown in other papers (Almeida et al(4), Holt et al(6)). In contrast to Penrose's(1) data of an increase in the frequency of thenar pattern in Turner's syndrome, Holt(6) and Forbes(5) did not find it. The frequency of thenar patterns in our Turner's was 0% compared to 6% and 8% in the normal males and males.

6) *Frequency of the simian crease per case*

Uchida et al(6) and Forbes(5) have found a frequency of about 13% and 17% respectively of simian crease in Turner's compared to 2% in the normal control population. Our survey shows that the simian crease was found in 25% of the XO cases and in none of the other sex-chromosome Turner's patients making up 10% of all the cases, compared to 2% of both control groups. (see Table VIII and Fif. 5).

TABLE VII

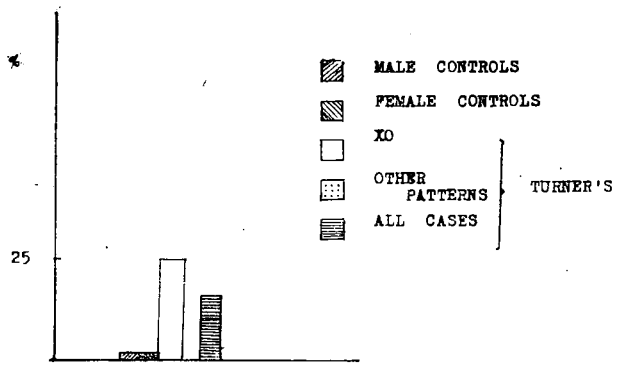
FREQUENCY OF SIMIAN CREASE IN PATIENTS WITH TURNER'S SYNDROME AND IN CONTROLS

MALES AND FEMALES

| GROUPS | CHROMOSOME PATTERN | Nº OF CASES | LEFT HAND | RIGHT HAND | BOTH HAND | TOTAL |
|---|---|---|---|---|---|---|
| TURNER'S SYNDROME | XO | 16 | 2 | - | 2 | 4 (25%) |
| | XO/XX XO/XX/XXX XO/XX$^{f}$ XO/XX$^{f}$/XX$^{i}$/XX XX$^{d}$ XX$^{i}$ XO/XY | 9 | - | - | - | - |
| | ALL CASES | 25 | - | - | - | 4 (16%) |
| CONTROL | NORMAL MALES | 50 | - | - | 1 | 1 (2%) |
| | NORMAL FEMALES | 50 | - | - | 1 | 1 (2%) |

7) and 8) No absence of distal triradii or any increased frequency of fusions of the distal triradii was found in the Turner's. The frequency of true interdigital patterns occurred in the Turner's patients with normal frequency.

FREQUENCY OF SIMIAN CREASE IN PATIENTS WITH TURNER'S SYNDROME AND IN CONTROLS MALES AND FEMALES




RESULTS OF THE SIGNIFICANT TESTS FOR DIFFERENCES BETWEEN MEAN VALUES IN TURNER'S SYNDROME AND IN CONTROLS MALES AND FEMALES

TABLE VIII

| | | | | t | DF | SIGNIFICANCE TEST |
|---|---|---|---|---|---|---|
| FINGER PRINTS ANALYSIS | DERMAL RIDGE COUNT PER DIGITAL PATTERN | TOTAL FINGER RIDGE COUNT | | TURNER'S/MALE CONTROL | 3.21 | 67 | HIGHLY SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 3.20 | 67 | HIGHLY SIGNIFICANT |
| | | | | XO/OTHER TURNER'S | 0.74 | 36 | NOT SIGNIFICANT |
| | | | WHORL | TURNER'S/MALE CONTROL | 2.62 | 157 | HIGHLY SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 2.04 | 116 | NOT SIGNIFICANT |
| | | | DOUBLE LOOP | TURNER'S/MALE CONTROL | 7.7 | 37 | HIGHLY SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 4.6 | 37 | HIGHLY SIGNIFICANT |
| | | | ULNAR LOOP | TURNER'S/MALE CONTROL | 4.9 | 420 | HIGHLY SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 4.8 | 469 | HIGHLY SIGNIFICANT |
| | | | RADIAL LOOP | TURNER'S/MALE CONTROL | 0.37 | 27 | NOT SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 0.06 | 14 | NOT SIGNIFICANT |
| PALM PRINTS ANALYSIS | a b RIDGE COUNT | | | TURNER'S/MALE CONTROL | 4.72 | 148 | HIGHLY SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 3.32 | 148 | HIGHLY SIGNIFICANT |
| | | | | XO/OTHER TURNER'S | 0.62 | 48 | NOT SIGNIFICANT |
| | MAXIMUM ATD ANGLE | | | TURNER'S/MALE CONTROL | 4.07 | 148 | HIGHLY SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 4.18 | 148 | HIGHLY SIGNIFICANT |
| | | | | XO/OTHER TURNER'S | 0.55 | 48 | NOT SIGNIFICANT |
| | t POSITION MEASUREMENT | | | TURNER'S/MALE CONTROL | 3.354 | 148 | HIGHLY SIGNIFICANT |
| | | | | TURNER'S/FEMALE CONTROL | 3.99 | 148 | HIGHLY SIGNIFICANT |
| | | | | XO/OTHER TURNER'S | 1.45 | 48 | NOT SIGNIFICANT |

## CONCLUSIONS:

The main dermatoglyphic findings in our series confirm the previous works on the field showing significant dermatoglyphic differences between patients with Turner's and normal controls male and female (see Table VIII).

The small number and non uniform pattern of other Turner's different from XO sex-Chromosome patterns and the impossibility of ruling out mosaicism in the XO considered cases do not allow further considerations about dermatoglyphic differences between the XO and other Turner's cases. Even so, for the main dermatoglyphic findings: total finger ridge count, atd angle, t position an a-b rigde count no significant statistical was found between the "pure" XO considered cases and the others.

## ACENOWLEDGMENT:

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## ASTRACT

The authors present the results of 19 finger-prints analysis and 25 palm-prints analysis in Turner's Syndrome and compare them to 50 normal male and 50 normal female controls. The main dermatoglyphic features of Turner's Syndrome found were: a higher total finger ridge count due to an increase in the number of ridges per different patterns, a raised maximum atd angle, a raised value of t position measurement, an increase in the frequency of both hypothenar pattern and simian crease and a significant finding of an unusual direction of palmar a and t lines.

## SUMÁRIO

Os autores estudaram as impressões digitais de 19 e as palmares de 25 pacientes com Sindrome de Turner e compararam os resultados com 50 controles masculinos e 50 contrôles feminimos. Os achados dermatoglíficos mais característicos da Síndrome de Turner foram: um aumento do número total de cristas dérmicas digitais, devido a um número maior de cristas dérmicas nos diferentes padrões, um valor mais elevado do ângulo atd e da medida da posição de t, um número maior de cristas dérmicas entre os deltas palmares a-b, um aumento na freqüência de impressões hipotenares e da prega simiesca e o achado muito frequente de trajeto anômalo das linhas palmares a e t.

*Arq. Bras. Endocrin. Metab.*, 16(3):163-172
*Dezembro* 1967, *Rio de Janeiro, Guanabara*

# CONTRIBUIÇÃO AO ESTUDO DOS ANABOLIZANTES EM HIPERLIPOPROTEINEMIAS

EVALDO MELO, NELSON LEON, EDISON N. GENTA, ANTONIO COELHO NETO, BERNARDO WAJCHENBERG, JULIO TIMONER (*)

Os efeitos dos androgênios sôbre o metabolismo lipídico são discutidos com bastante conflito na literatura (5,18). Para unificar as divergências dos achados metabólicos Olson e Vester admitiram que perante estado nutritivo adequado haveria com o uso de androgênios aumento das betalipoproteinas séricas e em carência poderia haver uma ação hipocolesterolemizante. O anabolismo dos péptides das betalipoproteinas seria reduzido quando houvesse deficiência de proteinas na dieta. (16).

Acreditamos, contudo, que as diferenças metabólicas não dependem exclusivamente do estado nutricional.

Utilizamos nesta investigação pacientes em bom estado nutritivo, com dieta normal, verificando que as diferenças metabólicas sôbre a influência dos androgênicos dependiam primàriamente da condição dos pacientes e das vias de ação dêstes esteróides.

Os dados observados não vieram justificar a interpretação de Robinson e col. (17) de que haveria progressiva hipercoles-

(*) Trabalho realizado na 13.ª Cadeira da Faculdade de Medicina da Universidade de São Paulo. (Serviço do Prof. A.B. Ulhôa Cintra).

terolemia nos seguintes estados: hiperestrogenismo → normoestrogenismo → hipogonadismo → normoandrogenismo → hiperandrogenismo.

## MATERIAL E MÉTODOS

Estudou-se 24 pacientes: oito mixedematosos, dois do sexo masculino e três portadores de Moléstia de Sheehan; três com síndrome nefrótica, todos com quadro histopatológico de glomérulonefrite membranosa; nove pacientes em fase de climatério, três delas normais, três com discreta hiperlipidemia sem causa determinada e três com diabetes mellitus controlado com administração de orilsufoniluréias; quatro pacientes com dislipidemias severas: J. M. C., 45 anos, fem. com hiperbetalipoproteinemia; G. J., 38 anos, masc. com hiperprebetaliproteinemia e Diabetes Mellitus tipo latente; O. A. S., 37 anos, masc. com hiperquilomicremia.

Os pacientes mixedematosos e os portadores de síndrome nefrótica foram estudados debaixo de hospitalização. Todos os pacientes foram submetidos à dieta geral com cêrca de 30 a 40% do total calórico como gordura; os nefróticos foram submetidos à dieta hipocloretada.

Não foram usadas medicações concomitantes e os pacientes foram observados em período contrôle maior ou igual ao experimental.

O estudo iniciado em maio de 1959 foi prosseguido sob forma de 32 cursos terapêuticos com duração média de 18 dias (6 a 30 dias). Utilizou-se a 1-deidro-17-α-metiltestosterona ou metandrostenolona (DMT) nas doses de 50mg/dia (13 cursos terapêuticos) e 100mg/dia (2 cursos); a metiltestosterona foi empregada nas doses de 25mg/dia (13 cursos) e 50mg/dia (2 cursos).

Determinou-se: a turbidez sérica expressa em unidades de lactescência contra blank de água; os lípides totais (14); o colesterol sérico total (4); os fosfolípides expressos em mg. de fósforo (21) e o perfil eletroforético (11).

Os dados foram analizados estatìsticamente segundo os critérios de Snedecor (19), adotando-se como nível de significância $\alpha = 0.05$.

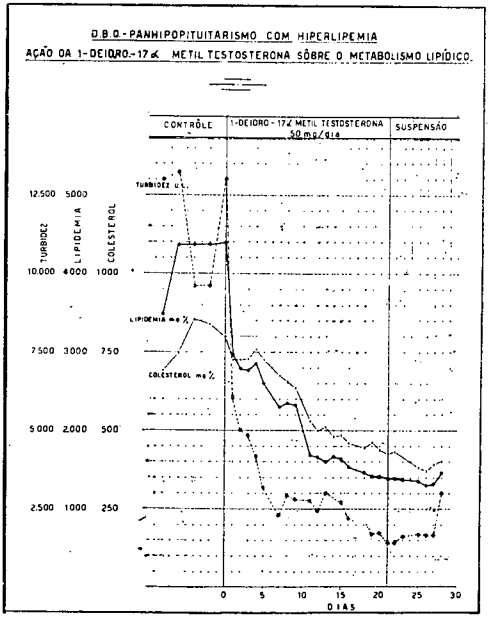
## RESULTADOS

A tabela I mostra a análise global da resposta terapêutica nos portadores de hipotireoidismo. Sete dêstes oito pacientes

| Períodos / Índices | DMT 50 mg/dia | | MT 25 e 50 mg/dia | |
|---|---|---|---|---|
| | Contrôle | Experimental | Contrôle | Experimental |
| TURBIDEZ u.l | 3481 ± 1420 | 803 ± 160 ** | 3402 ± 780 | 1236 ± 505 ** |
| LÍPIDES mg% | 1769 ± 520 | 960 ± 270 ** | 1356 ± 243 | 809 ± 193 ** |
| COLESTEROL mg% | 381 ± 73 | 308 ± 81 * | 335 ± 53 | 268 ± 53 ** |

Efeito da Metandrostenolona (DMT) e da Metiltestosterona (MT) sôbre os lípides séricos de mixedematosos, em cursos terapêuticos de 12 dias, em média. Resultados expressos como $\bar{x} \pm s$.

*Diferença significativa ao nível de $\alpha = 0,05$
**" " " " " $\alpha = 0,01$

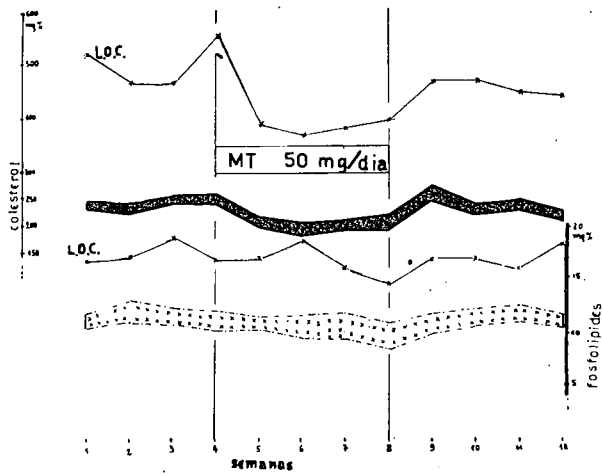


responderam com progressivo decréscimo da lipidemia e da lactescência. Os índices estudados mostraram queda proporcional, como ilustra a fig. 1, mas a colesterolemia mostrou maior resistência (resposta significativa em 6 de 15 cursos).

| Índices \ Períodos | Contrôle | Experimental |
|---|---|---|
| TURBIDEZ | 429,4 ± 62,7 | 393,3 ± 42,5 |
| LÍPIDES | 723,2 ± 113,0 | 674,6 ± 140,0 |
| COLESTEROL | 247,0 ± 30,3 | 210,7 ± 45,0 * |
| FOSFOLÍPIDES | 11,2 ± 1,34 | 9,8 ± 1,88 * |
| COLESTEROL / FOSFOLIPIDES | 0,87 ± 0,108 | 0,83 ± 0,034 |

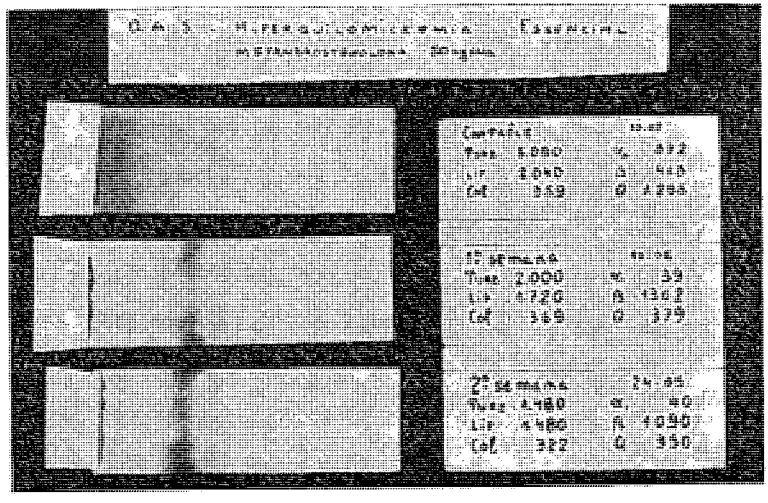
Efeito sôbre os lípides séricos da Metiltestosterona na dose de 25 mg/dia, durante 30 dias, em nove pacientes menopausadas. Resultados expressos como $\bar{x} \pm s$

*Diferença significativa ao nível de $\alpha = 0,05$.

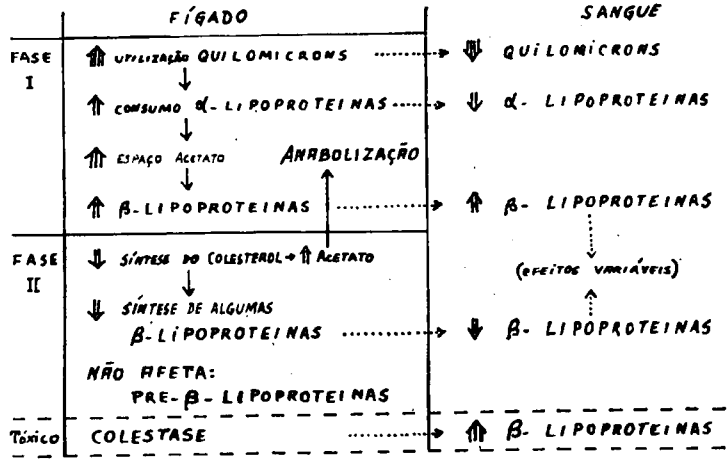



Dois de três portadores de síndrome nefrótica mostraram incremento da colesterolemia (20 e 31%); no terceiro paciente não houve qualquer ação.

A metiltestosterona provocou decréscimo significativo do colesterol e dos fosfolípides totais, sem modificar a relação colesterol/fosfolípides (Tabela II). O efeito sôbre o colesterol ocorreu na primeira semana de tratamento, sem modificação no restante do período experimental (fig. 2). Observou-se queda da colesterolemia (20 a 27%) em 5 dos 9 pacientes.



INTERPRETAÇÃO DA AÇÃO DOS ANDROGÊNICOS SÔBRE OS LÍPIDES



Não responderam à metandrostenolona o paciente J. M. C. com hiperprebeta e hiperbetalipoproteinemia e o paciente G. J. com hiperprebeta-lipoproteinemia. A paciente L. O. C. portadora de hiperbetalipoproteinemia, mostrou queda da colesterolemia (fig. 2) com a metiltestosterona. O portador de hiperquilomicremia — O.A.S. — apresentou com a metandrostenolona queda de turbidez e da lipidemia, com redução das alfalipoproteinas e dos quilomicrons, com concomitante incremento das betalipoproteinas (fig. 3).

## DISCUSSÃO

É habitual na literatura a afirmação da ação hipocolesterolemizante dos estrógenos e hiperlipidemizante dos andrógenos; a administração de progesterona resultou em alterações equívocas nas concentrações dos lípides circulantes (15,16).

Furman e col (12), Cohen e col (6), Castillo e col. (5), Campbell e col. (3) e, no Brasil, Vaissman, Cantisano e Granato (20) demonstraram o efeito hipocolesterolemizante dos hormônios androgênicos.

Os nossos resultados mostram que, em cursos terapêuticos de 6 a 30 dias, a metandrostenolona e metiltestosterona provocam um efeito hipolipidemizante, não necessàriamente com queda significativa da colesterolemia.

Os portadores de hipotireoidismo mostram predominantemente queda da concentração dos glicérides, desde que a turbidez é um índice que reflete betalipoproteinas ricas em glicérides e quilomicrons (1). A redução média da colesterolemia, com êstes esteróides, foi de 20 a 30% em relação ao período contrôle, enquanto que a lipidemia total e a turbidez cairam, no mínimo, 34% e 64%, respectivamente, com o tratamento anabolizante.

A redução dos triglicérides com os anabolizantes foi, também, verificada por Howard e Furman com as formas pirazólicas da metilandrostana e do metilandrosteno (12).

Fica, portanto, uma interrogação sôbre o mecanismo da redução dos glicérides séricos sob a influência dos androgênicos.

Olson e Vester (16) afastaram a possibilidade da interferência do tecido adiposo por não existir alteração significativa dos NEFA com uso dêstes esteróides.

A participação do fígado na utilização dos glicérides é bem conhecida (9). Sabe-se, de outro lado, que as alfalipoproteinas participam para esta utilização. Pode-se esperar, portanto, uma redução das alfalipoproteinas séricas com o aumento da utilização das lipoproteinas ricas em glicérides. Foi o que verificamos no paciente O. A. S., portador de hiperquilomicremia. A administração de metandrostenolona provocou decréscimo dos lípides totais concomitante com o decréscimo dos quilomicrons e das alfalipoproteinas. Espera-se, também, que a utilização de quilomicrons pelo fígado provoque um incremento do espaço acetato hepático e que êste possa ser utilizado na síntese de betalipoproteinas. Em realidade, no paciente O.A.S., ocorreu um magnífico incremento das betalipoproteinas, uma verdadeira interconversão de quilomicrons e alfalipoproteinas em betalipoproteinas. Esta interconversão das lipoproteinas, com decréscimo dos glicérides, ocorreu sem alteração significativa da colesterolemia.

Êstes dados sugerem, portanto, que uma fase importante da ação dos androgênios é o aumento da utilização dos glicérides, afetando em menor escala a concentração do colesterol sérico.

Há, contudo, em mixedematosos, em hiperbetalipoproteinemia (paciente L. O. C.) e em menopausadas uma ação hipocolesterolemizante dos esteróides androgênicos. A magnitude desta ação é menor, mas significativa. Acreditamos que o encontro de Fillions, e col. (8) mostrando uma menor velocidade de incorporação do acetato C14 no espaço colesterol hepático em ratos machos ou com a administração de andrógenos explica a hipocolesterolemia com êstes esteróides. Esta atividade dos andrógenos deve ser inconstante e, provàvelmente não reduz a formação do colesterol para algumas lipoproteinas como as prebetalipoproteinas (pacientes J. M. C. e G. J.) e nas betalipoproteinas encontradas em portadores de Síndrome Nefrótica.

Na fig. 4 procuramos sintetizar uma interpretação provável da ação dos androgênios sôbre os lípides. A fase I representaria a ação dos androgênios em pacientes com hipergliceridemia

(idiopática ou secundária ao hipotireoidismo). A fase II explicaria a ação dêstes esteróides em algumas colesterolemias (menopausa e hiperbetalipoproteinemia). Nota-se que foi destacada Hanabolização, pois é um fato bem claro nesta investigação e em outras o efeito anabolizante dêstes esteróides.

Admitimos que a fase I e II possam aparecer isoladas ou combinadas no mesmo paciente. Este evento parece depender das condições basais do doente; em hipergliceridemia idiopática teríamos predominantemente a fase I; em mixedematosos a fase I a fase II ou ambas; em hipercolesterolemia a fase II; em Síndrome Nefrótica e outras condições teríamos uma fase II ineficiente.

Deve-se ressaltar que é sempre possível, principalmente com esteróides 17-metilados o aparecimento de colestase com efeito hipercolesterolemizante de natureza tóxica (2). É esta a nossa hipótese para a casuística de José e Mitchell a que empregaram a metandrostenolona, na dose de 15mg/dia, durante 12 semanas. Observaram em 5 pacientes um incremento médio da colesterolemia de 351 para 405mg% (13).

Os androgênios utilizados foram eficientes por via oral, com comportamento bem diferente da androsterona que é inativa por esta via e muito eficiente por via intramuscular (6).

Quanto ao chamado "efeito tireomimético dos andrógenos" é aconselhável abandonar esta expressão de Hellman e col. (10). Há na realidade uma deficiência de androsterona em hipotireoidismo e em hipercolesterolemia (7). A correção do hipotireoidismo ou o excesso de hormônio tireoidiano aumentam a produção de androsterona (10).

Não foram verificadas diferenças substanciais entre a metandrostenolona e a metiltestosterona na ação sôbre os lípides séricos.

## SUMÁRIO

Utilizou-se, por via oral, a metandrostenolona (50 e 100 mg/dia) e a metiltestosterona (25 e 50 mg/dia) em 24 pacientes, sob a forma de 32 cursos terapêuticos com duração média de 18 dias.

Houve diferenças na qualidade de resposta conforme a patologia básica do paciente: mixedematosos (8 casos) e hiperquilomicremia

idiopática responderam principalmente com redução de glicérides; menopausadas (9 casos) e hiperbetalipoproteinemia responderam com redução da colesterolemia; nefróticos (3) e pacientes com hiperprebetalipoproteinemia (2) não responderam às drogas.

Intepretou-se êstes resultados admitindo-se que a condição dos pacientes acarretaria diferenças nas vias metabólicas da ação androgênica sôbre os lípides (Fig. 4). A interpretação sugerida permite compreender os conflitos de resultados observados na literatura médica.

## SUMMARY

Methandrostenolone (50-100 mg/day) and methyltestosterone (25-50 mg/day) were given to 24 patients; a total of thirty two therapeutical courses with an average duration of 18 days, were followed.

There was a decrease in serum glycerides in the eight patients with myxedema and in the patient with idiopathic hyperchylomicronemia; a reduction in serum cholesterol was observed in the nine post-menopausal womem; no significant response was seen in the three nephorotic patients and in two patients with hyperprebetalipoproteinemia.

We suggest that the androgenic hormone atc on different metabolic pathways in accordance to the patients disease (Fig. 4), and this suggestion would explain the conflicting results observed in the medical literature.

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months after he started to gain weight progressively. At the same time his face became rounded, reddish and studded with acne. Shortly afterwards there was a progressive increase in size of the genitalia, which rapidly evolved to the adolescent stage, while the patient's voice became low-pitched and hair appeared over his face and body. Two months before admission ankle edema was noticed. This became generalized later on, while shortness of breath developed. There was a constant complaint of headache. Shortly before admission a progressive increase in size of the abdomen became evident.

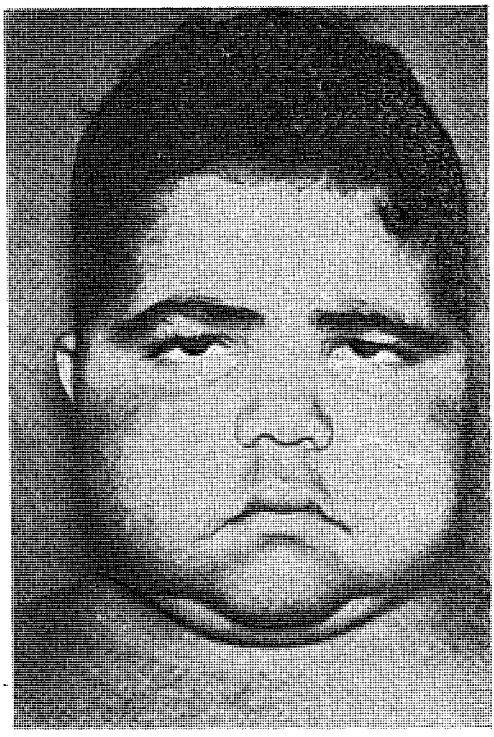

Figure 1 — The patient before operation.

Past history was non-contributory. During pregnancy the patient's mother was given progesterone to check a tendency to abortion.

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# TESTICULAR MATURATION IN ADRENAL HYPERFUNCTION (*)

J. S. DE OLIVEIRA COUTINHO, M. BARRETTO NETTO, J. A. ALBUQUERQUE LINS, H. SALTI, CLAUDIO SOUZA LEITE

It is a well-known fact that adrenocortical tumours may cause a mixed type of hyperfunction, affecting both cortisol and androgen production. The resulting clinical picture combines manifestations of Cushing's and adrenogenital syndromes. It is also known that both syndromes when they have their onset during childhood usually result from adrenal cortex malignancy (1). All that was found in the present case. But what makes it rather exceptional and interesting enough for publication is the unequivocal evidence of hatrue precocious puberty, resulting from testicular maturation and associated with well proved adrenal hyperfunction.

## CASE REPORT

The patient, a 5-year-old boy, was admitted with the chief complaint of a profound change in his body shape. When he was 2½ years old pubic hair growth was first noticed. Six

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Physical examination revealed a boy chronically ill, normally tall, obese but showing comparatively thin limbs. Height was 3 foot 3 inches, weight 54 lbs. Several, sparse ecchymoses were noticeable. A full-moon, reddish, hairy and acne studded face (Fig. 1), a hairy chest, a fat pad (bufalo hump) on the back of the neck were among the chief findings of physical

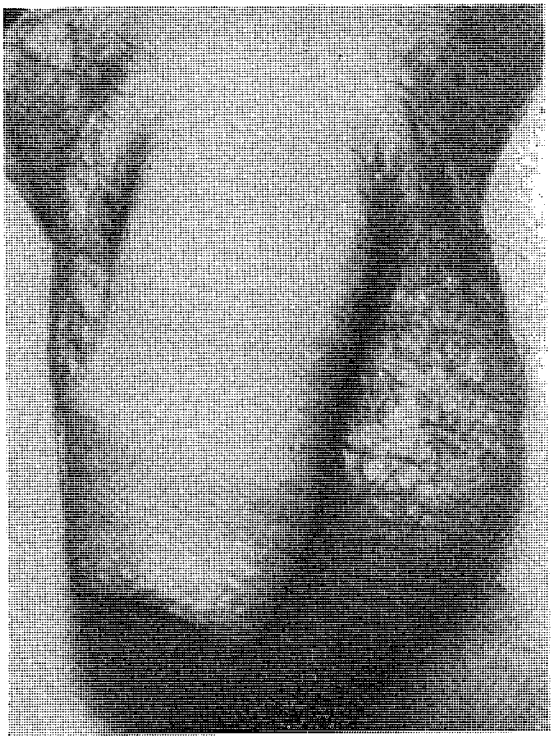

Figure 2 — The patient's external genitalia.

examination. On a thick, bulging abdomen, a hard, large mass was evident on the right upper quadrant. Umpalpable spleen. Blood pressure was 190/130 mm Hg, pulse rate 88, heart sounds were loud. Adolescent genitalia, with the presence of pubic hair, a 6-centimeter-long penis and 3.5-centimeter-long testes (Fig. 2). Eye grounds: thin, pale and straightened arteries.

Laboratory findings — RBC 5.930.000/mm³. Blood sugar 80 mg%. Sodium 126 m.Eq./1. Choloride 107 m.Eq./1. Potassium 3.7 m.Eq./1.

An intravenous pyelogram revealed a large, partially calcified retroperitonial mass pushing the right kidney downwards. X-ray of the vertebrae showed evidence of osteoporosis. Bone age was 9 years.

| | |
|---|---|
| Urinary hormone tests | |
| 17-OH corticosteroids (Reddy) | |
| Basal | 56 mg/24-hour urine |
| After dexamethasone (8 mg daily, 48 hours) | 60 mg |
| 17-KS (Oesting & Callow) e | |
| Basal | 216 mg/24-hour urine |
| After dexamethasone (8 mg daily, 48 hours) | 238 mg |
| Chromatographic analysis | |
| Fractions I & II | 18 mg |
| Fraction III (Beta 17-KS) | 72 mg |
| Fraction IV (androsterone) | 54 mg |
| Fraction V (etiocholanolone) | 30 mg |
| Fractions VI & VII (11-oxy 17 -KS) | 18 mg |
| Fraction VIII | 12 mg |
| Total | 204 mg/24-hour urine |
| FSH | 16 M.U./24-hour urine |

Clinical course — An attempt to eradicate the clinically diagnosed tumour was decided upon. At operation a 960-gram retroperitonial, encapsulated tumour was removed, which was shown to be a carcinoma of the right adrenal. After operation an almost complete regression of the patient's abnormal findings was observed (Fig 3). Blood pressure dropped to 82/60 mm Hg, 17-OH to 4.2 mg and 17-KS to 4 mg/24-hour urine, The patient was discharged two months after operation. Four months later, however, a progressive return to his former condition was apparent, while the presence of a large, hard mass on the right upper quadrant of the abdomen became again evident. Urinary 17-OH-CS rose to 232 mg and 17-KS to 691

mg/24-hour urine. The patient was again admitted to the hospital. Three weeks later he had severe intestinal haemorrhage and died suddenly.

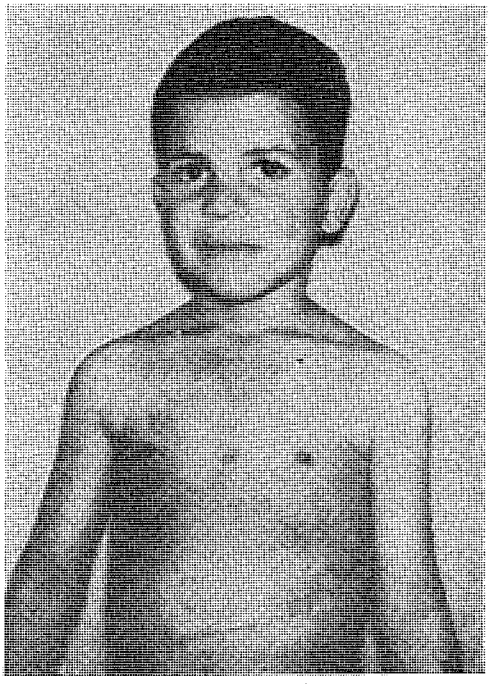

Figure 3 — The patint after operation.

Pathology findings — Against the upper half of the right kidney a large tumour mass was present, which was shown at microscopy to be an adrenocortical carcinoma (Fig. 4). The left adrenal was atrophic. Adult sized testes, which at microscopy revealed well developed seminiferous tubules, with patent lumina, spermatogonia and primary spermatocytes, Sertoli and Leydig cells (Fig. 5). The prostate showed well differentiated glandular tissue. Microscopy of the pituitary revealed only the presence of large basophilic cells, with normal eosinophilic and chromophobe cells. Causa mortis: mesenteric infarction.

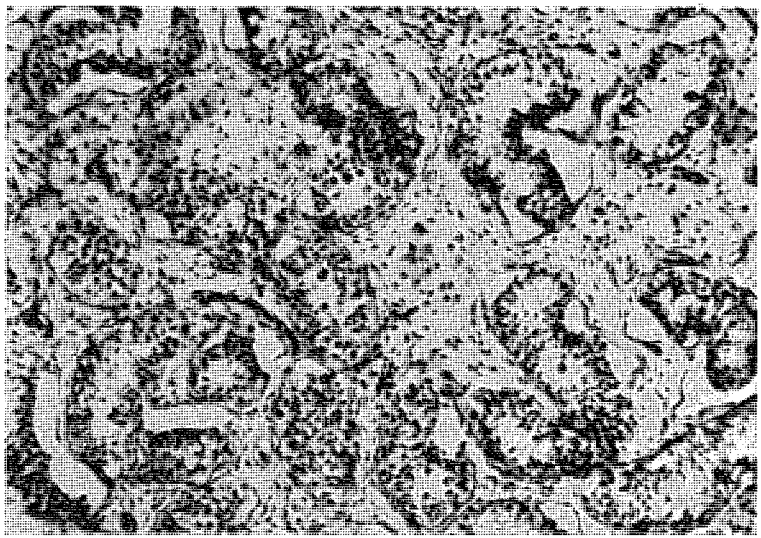

Fig. 4 — Microscopic aspect of the adrenocortical carcinoma.

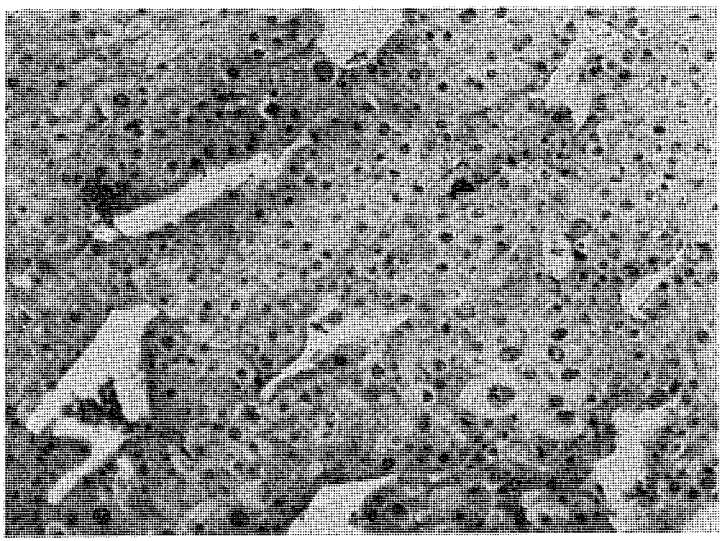

Figure 5 — Prepubertal testes showing well developed seminiferous tubules with patent lumina, spermatogonia and primary spermatocytes, Sertoli and Leydig cells.

## DISCUSSION

The patient's clinical picture established beyond any doubt the existence of a mixed adrenocortical hyperfunction, with signs and symptoms of Cushing's syndrome resulting from cortisol overproduction, and an andrenogenital syndrome associated with androgen hypersecretion. Bot physical examination and laboratory findings confirmed this diagnosis. On the other hand, the presence of a large, hard abdominal mass, palpable on the right upper quadrant, the intravenous pyelogram and the negative dexamethasone suppression test proved that adrenal hyperfunction was caused by a tumour. Its existence was surgically and pathologically confirmed.

As pointed out before' the association of testicular maturation with adrenocortical hyperfunction, although previously mentioned in the literature (2), is an interesting feature of the case. In fact, the patient had a true precocious puberty proved by: (a) size and consistency of the testes; (b) its histological aspect and (c) FSH level.

The following hypotheses should be considered in connection with the patients's testicular maturation:

1) Androgen action on spermatogenesis. It is a well-known fact that testosterone is partially responsible for the maintenance of spermatogenesis. The testes size and its well developed seminiferous tubules might be partially explained as a direct result of the high level of circulating adrenal androgens. Nevertheless, the development of Leydig cells and FSH level proved that we were not facing testicular enlargement and precocious spermatogenesis only, but testicular maturation consequent to gonadotropic stimulation.

2) Hypothalamic metastases effect on gonadotropic stimulation. Brains metastases of adrenal carcinoma have been described. Such metastases, if present, might have started gonadotropin secretion and gonadal stimulation. Pathological findings, however, disproved this hypothesis.

3) Adrenocortical hyperfunction causing gonadal stimulation. Landing & Gold (3), Escamilla (4) and Kovacic (5) presented data showing the occurrence of precocious gonado-

tropin secretion in cases of congenital adrenal hyperplasia. According to their findings one can postulate adrenal androgens as responsible for anterior pituitary stimulation and precocious gonadotropin production in the studied cases. On the other hand, Sohval & Soffer (6) found FSH increased in patients receiving corticoid and ACTH therapy, whence it might be inferred that cortisol has also the capacity to trigger gonadotropin secretion. These findings would lead one to admit that adrenocortical hyperfunction may cause anterior pituitary stimulation, although this is contrary to the general belief which atributes the amenorrhea of Cushing's syndrome to gonadotropin inhibition.

4) Direct action of the adrenal tumour on the tests. In an adrenal tumour Reifenstein (7) found the presence of gonadotropin. On the other hand, McFadzean (8) and Chambers (9) presented cases of adrenocortical carcinoma in which there was a positive Friedman test. The well-known production of hormones by tumours arising from tissues not related to their normal secretion, may make acceptable the possibility of an adrenocortical carcinoma producing a gonadotropin-like substance.

At any rate it seems clear that the hyperfunctioning and tumourous adrenal, acting indirectly on the anterior pituitary or directly upon the gonads, caused testicular maturation in our case.

RESUMO

Os autores apresentam um caso de puberdade precoce num paciente portador de hiperfunção córtico suprarrenália. Feita a laparotomia foi evidenciada a presença de um carcinoma de Supra-Renal que levou o paciente à morte.

O tamanho e a consistência dos testículos, sua histologia e os níveis urinários de gonadotrofinas não deixam margem a dúvidas quanto à existência de um processo de maturação gonadal.

Quatro hipóteses são formuladas no sentido de se explicar tal achado. Assim uma ação androgênica, na espermatogênese, matastases hipotalâmicas estimulantes da secreção de gonadotrofinas, à hiperfunção da córtex da suprarrenal causando estímulo gonadal ou uma ação direta do tumor sôbre o testículo, seriam os mecanismos a serem discutidos na etiopatogenia de tal achado.

SUMMARY

An unusual true precocious puberty in a case of adrenocortical hyperfunction is presented. On operation a carcinoma of the right adrenal was found, which recurred and caused the patient's death. Testicular maturation associated with mixed adrenocortical hyperfunction was proved by: (a) size and consistency of the testes; (b) its histology and (c) the urinary gonadotropin level. Possible explanations for these facts are discussed.

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# A SIMPLE TECHNIQUE FOR SEPARATION OF CORTISOL METABOLITES BY THIN-LAYER CHROMATOGRAPHY AND ITS APPLICATION FOR THE MEASUREMENT OF CORTISOL SECRETION RATE (*)

REGINALDO H. ALBUQUERQUE** and BERNARDO LÉO WAJCHENBERG

Since the advent of thin-layer chromatography several methods have been suggested for the rapid and accurate separation of steroids (1-8). However, the separation of urinary 17-hydroxy-corticosteroids (17-OH CS) by thin-layer techniques has received little attention (9).

The technique described in this paper provides a simple, yet sensitive method for the separation of individual urinary 17-OH CS which can be applied for the measurement of cortisol secretion rate.

## MATERIAL AND METHODS

The Desaga/Brinkmann apparatus for thin-layer chromatography was employed. All chemicals were of analytical grade

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and the solvents were redistilled prior to use. Steroid reference compounds(*) were obtained from Mann Research Laboratories, Inc, New York City. A gift of tetrahydrocortisone was received from Dr. John S. Tzoumertis, Merck, Sharp & Dohme Research Laboratories, Rahway, N. J.. The steroid standards were dissolved in 95% ethanol (10 ug/ml.) and kept in deep-freeze.

*Collection and storage of urine*: Urine was collected for 24-hour periods and kept in the ice box, without preservative and analyzed while fresh. An aliquot of the 24-hour urine collection was brought to PH 6 with 0.5N acetic acid or 1N sodium hydroxide.

*Extraction, hydrolysis and washing procedures:* A known aliquot of a 24-hour urine collection, usually between 0,05 and 0.2 of the total volume, was extracted with 2 — 3 volumes of dichloromethane, two to three time, toremove the free (unconjugated) steroids.

After extraction of the free steroids, 0.1 volume of 5M sodium acetate buffer of pH 5 and $\beta$-glucuronidase (**) to a final concentration of 1,000 unit/ml, are added. After incubation at 47°C overnight, the liberated steroids were extracted with 3 x 4 volumes of ethyl acetate. The combined extracts were washed with 0.5N sodium hydroxide (3 x 0.5 volume) followed by 0.05 vol. of water.

After addition of anhydrous sodium sulfate, the extract was filtered and reduced to a volume of about 5 ml. after evaporation at 45°C under pressure. It was then quantitatively transferred into a 15 conical test tube and evaporated to dryness on a water bath under blowing nitrogen. The dry residue is then redissolved in 0.2ml of absolute ethanol and a known aliquot applied with a micro pipette to the plate.

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* The following abreviations and trivial names are used: F = cortisol 4-pregnen-11 $\beta$, 17 $\alpha$, 21-triol-3, 20-dione) E = cortisone (4-pregnen-17 $\alpha$, 21-diol-3, 11, 20-trione) THE = tetrahydrocortisone (5$\beta$ — pregnan-3 $\alpha$, 17 $\alpha$, 21-triol-11, 20-dione). THF = tetrahydrocortisol (5$\beta$ — pregnen-3 $\alpha$, 11$\beta$, 17 $\alpha$, 21-tetrol-20-one).

** Ketodase — Warner — Chilcott.

*Preparation of the chromatoplates*: The glass plates, 20 x 20 cm were thoroughly cleaned, rinsed with water and dried in an oven. 30 g silica gel G was added to 50 ml distilled water and mixed approximately 1 1/2 min. The slurry was poured into the reservoir of a chromatofilm spreader calibrated to give a layer of adsorbent 250 $\mu$ in thickness and spread in a single continuous movement. The plates were allowed to set overnight and then activated at 110°C for 1 hour. They were then stored in a vaccum desiccator.

*Chromatography*: Aliquots of the urine extract and the steroid standards were applied in the plates, which were placed in Brinkmann developing tanks (12 by 3 7/8 by 10 7/8 inches), lined with a double layer of Whatman No.1 filter paper to a distance of 1 cm from the top. The chromatographic development was unidimensional, ascending, in a chloroform: ethanol: water (90:10:1) system. When the solvents had ascended the plates for a distance of 16 cm, they were removed from the tank and allowed to air-dry. The plates were sprayed with blue tetrazolium (two parts of 0.2% aqueous blue tetrazolium and one part of 10% sodium hydroxide, freshly prepared) and the urinary stercids present were identified by their position in reference to the standards on the plate. Plates were always prepared in duplicate, one for visualization of the quantitative plate containing the urinary steroids was shielded and the edges containing the standards were sprayed. The plate was then superimposed on the transluminated sprayed duplicate and the standards of both plates were alligned. This technique allowed accurate localization of the position as well as the size of the unknown spots tobe quantitated.

The adso rbent containing the steroids is removed from the plate mechanically with a micro model of a vaccum zone collector (obtained from Brinkmann Instruments, Westbury, New York).

The steroids are eluted with 3 x 5 ml absolute ethanol, and filtered on Whatman No. 42 paper, reduced to 5 ml. final volume under blowing nitrogen.

Quantitation was carried out by procedure of Porter and Silver ([10]).

Cortisol secretion rates were measured in 3 normal male subjects (aged 17, 28 and 59) and one Addisonian kept on 40 mg of cortisol daily, by isotope dilution using the technique described by Cope and Black([11]). A tracer dose of Cortisol — 4 — $C^{14}$ (1$\mu$c) was diluted with 40 ml of water and given orally. Urine was collected for the next 24 hours.

Aliquot of the 24-hour urine was counted** and correcting for self-absorption, the percentage of the administered dose excreted in the 24-hour period was calculated. In the same way, the $^{14}C$ content of the administered dose was determined. The specific activity of THE as counts per minute per microgram of the metabolite was determined.

The cortisol secretion rate was calculated using the formula for isotope dilution determination:

$$\text{Secretion rate (mg/day)} = \frac{\text{Dose of administered isotope (cpm)}}{\text{Specific acitivity of THE (cpm/ug)}} \times \frac{1}{1{,}000} \quad (1)$$

or

$$\text{Cortisol secretion rate} = \frac{\text{Total radioactivity in 24-hour urine sample}}{\text{Specific activity of THE}} \times \frac{1}{1{,}000} \quad (2)$$

The true secretion rate will lie between the two figures Dose/S.A.$_U$ (1) and $C_U$/S.A.$_U$ (2).

## *RESULTS AND DISCUSSION*

By employing our method it was possible to separate and identify several 17-OHCS, as shown in figure 1. The Rf. values

* Obtained from New England Nuclear Corp, specific activity 118 uc per mg and 100% purity.

** Nuclear Chicago, Model D47, gas flow counter.

of pure steroids, chromatographed singly and as mixtures, in the solvent system employed, are indicated in table 1.

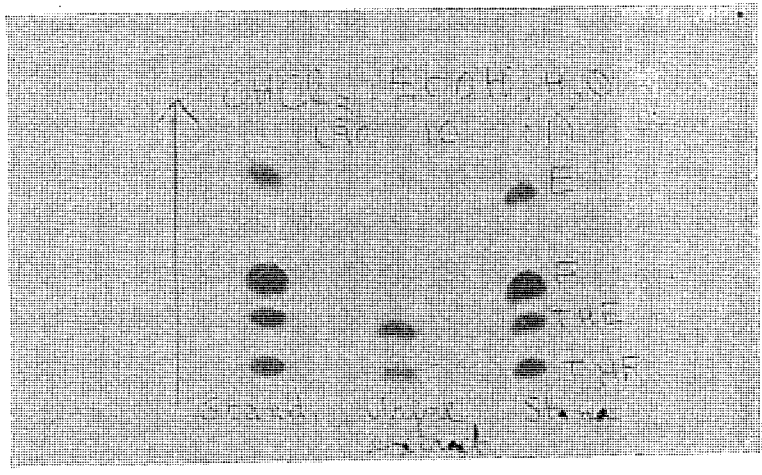

FIGURA 1 — Migration of 17-hydroxycorticosteroid standards and urine extract on silica G film in slovent system ō chloroform : ethanol : water.

*T A B L E 1*

MEAN Rf VALUES* OF 17-OHCS IN SOLVENT SYSTEM CHLOROFORM:

ETHANOL: WATER

| Steroid | Rf |
|---|---|
| THF | 0.31 |
| THE | 0.47 |
| F | 0.55 |
| E | 0.82 |

(*) Mean Rf value of 10 determinations.

In the urinary extracts blue tetrazolium spots corresponding to THE and THF were identified. An intermediary spot, was always present and probably was allo — THF ( 5α-pregnan 3α, 11β, 17α, 21- tetrol-20-one). Unfortunately, we were unable up to the moment to confirm this suggestion as no standard was available to us. Compounds F and E were not identified in the urinary extracts as they were extracted as unconjugated steroids.

The results of cortisol secretion rates are shown in TABLE 2

TABLE 2
CORTISOL SECRETION RATES

| Patient | Age and Sex | Weight Kg | Height cm | Estimated Cortisol Secretion Rate | |
|---|---|---|---|---|---|
| | | | | Dose/ S.A.$_U$ (mg/day) | $C_U$/ S.A.$_U$ (mg/day) |
| J.A.F. | 17 y,M | 56.1 | 168 | 14.8 | 14.0 |
| E.F. | 28 y,M | 68.4 | 174 | 16.5 | 14.1 |
| A.C. | 59 y,M | 61.3 | 163 | 8.5 | 7.5 |
| | | | | MEAN: 13.3 | 11.9 |
| J.D. * | 53 y,M | 61.4 | 171 | 37.4 | 31.6 |

* Addisonian maitained on 40 mg of cortisol/day

The mean cortisol secretion rate in the normal subjects was similar to that found by Cope and Black ([11, 12]). Besides, there is a good correspondence between our estimates of cortisol production by oral administration of $^{14}C$ — cortisol and the data in the literature based on I.V. administration of the tracer ([13,14]).

In patient J.D., having been on the same maintenance dose for several days, the calculated secretion rate (between 37,4 and 31,6 mg/day) agreed reasonably well with the known quantity of cortisol administered (40 mg/day). The excretion of 85% of the administered dose in the 24-hour urine sample speaks in

favour of completeness of absorption of the steroid and the reliability of the use of the oral route for the measurement of cortisol production rates, as about 90% of the tracer dose will be excreted in the urine, in the 24 hours after a single injection of the tracer[15].

SUMMARY

A technique of one-dimensional thin-layer chromatography on silica gel is described providing a simple, rapid and sensitive method for the separation and identification of individual urinary 17-hydroxycorticosteroids. Its application for the measurement of cortisol secretion rate by the isotope dilution method is indicated.

RESUMO

Os AA. descrevem um método de cromatografia em camada fina, uni-dimensional, rápido e sensível para separação e identificação dos 17 hidroxicorticosteroides urinários. Estabelecem ainda condições de coleta e armazenamento da urina, abordando a extração hidrólise e lavagem do material assim como o preparo das cromatoplacas e finalmente a cromatografia e a coloração das referidas placas.

O método descrito também é aplicável na análise do ritmo de secreção de cortisol pelo método de diluição isotópica o que foi feito em 3 indivíduos normais e em um paciente addisoniano.

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# HERMAFRODITISMO VERDADEIRO COM CARACTERÍSTICAS DE SÍNDROME DE KLINEFELTER (*)

HERMES PARDINI (**), VICTOR CORONHO (**), MOYSÉS PURISCH(**), JOSÉ CARLOS CABRAL DE ALMEIDA (***)

Casos de hermafroditismo verdadeiro apresentado características do sidrome de Klinefelter têm sido raramente referidos (1-7). Apresentamos neste trabalho um caso em que a referida associação se apresentou de modo ainda não relatado.

## *CASO E MÉTODOS*

A. A. D. (fig. 1), 25 anos, branco, solteiro, ginecomastia progressiva desde os 13 anos simultâneamente à direita e à esquerda. Penis pouco desenvolvido, tendo ejaculado pela primeira vez aproximadamente aos 12 anos. Barba escassa apareceu aos 17 anos, acompanhada de comedões e acne (fig. 2). É mais baixo que seus irmãos. Não sabe informar sôbre o seu crescimento na puberdade. Já manteve relações sexuais. Nega im-

(*) O presente caso foi estudado na 1.ª Cadeira de Clínica Médica, Setor de Endocrinologia — Serviço do Prof. Caio Benjamin Dias. Universidade Federal de Minas Gerais — Belo Horizonte.
(**) Assistentes de Ensino.
(***) Chefe da Unidade de Citogenética Humana — Instituto de Biofísica e 3.ª Cadeira de Clínica Médica — Universidade do Brasil — Rio de Janeiro — GB.

potência. Bom desenvolvimento intelectual, cursou o primário e a escola técnica. Nega orquite e irradiação genital. Não há história familiar de defeito genital ou hipogonadismo. Pais não são parentes e quando nasceu, o pai tinha 48 anos e a mãe 36 anos.

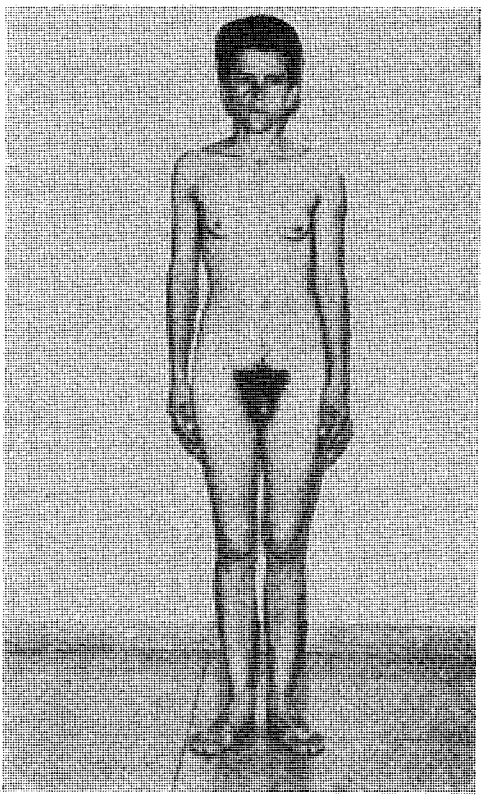

Fig. 1

*Exame Físico*: —

Pêso: 45,7 Kg. — altura: 157 cms. — envergadura 156 cms — distância pubis-planta: 84 cms. — distância pubisvertex:: 73 cms.

Hábito masculino, voz infantil, musculatura hipotônica e hipotrófica. Barba apenas mentoniana. Pêlos pubianos de distribuição masculina. Pêlos cefálicos com implantação masculina. Não há pêlos toráxicos, escassa pilosidade nos membros. Acentuada ginecomastia bilateral notadamente à direita com areola pigmentada e mamilos salientes (fi. 2). Penis medindo 5 cms

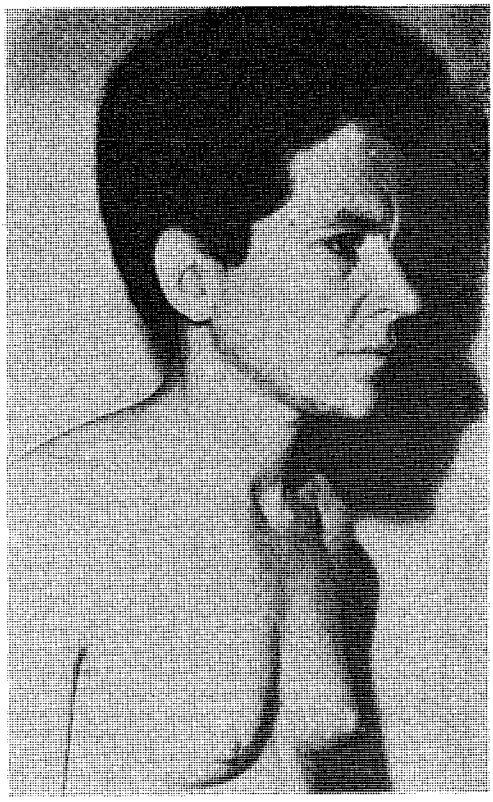

Fig. 2

de comprimento por 4 de circunferência. Uretra peniana sem hipospádia. Genitália pigmentada. Bolsas pregueadas com fusão mediana normal. Períneo normal. Gônadas nas bolsas, de pe-

queno tamanho (2 x 1 cms. cada) e de consistência firme (fig. 3). Próstata pequena, palpável. Visão para côres normal.

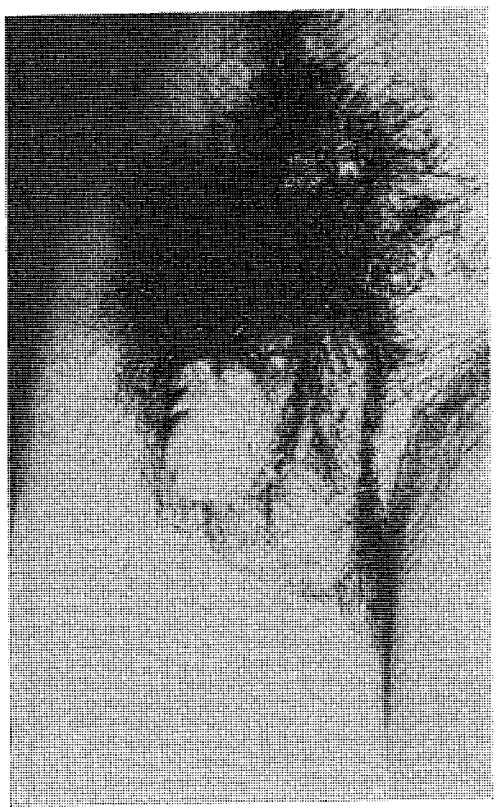

Fig. 3

*Exames Complementares*: —

Espermograma — 2 ml. de líquido inodoro, transparente com pH — 6 e viscosidade baixa. Ausência de espermatozoides e de células da maturação.

17 — cetosteróides urinários totais: — 9,1 mg/24 hs. e 9,6 mg/24 hs.

Gonadotrofinas hipofisárias (Caolin-Acetona): — Maior do que 90 e menor do que 120 M.U./24 hs. e maior do que 120 e menor do que 180 M.U./24 hs.

Cromatina nuclear oral foi positiva em 47% das células.

Biópsia Gonadal: —

Gônada esquerda: — intensa e difusa hialinose e esclerose tubular. Poucos tubulos seminiferos apresentavam luz visivel com ràros elementos intratubulares. Hiperplasia das células de Leydig de tipo adenomatoso (fig. 4). Um foliculo de Graaf típico, envolvido por estroma ovariano foi achado contendo (fig. 5) dois corpusculos de Call-Exner (fig. 6). Foi achado também um folículo primordial (fig. 7).

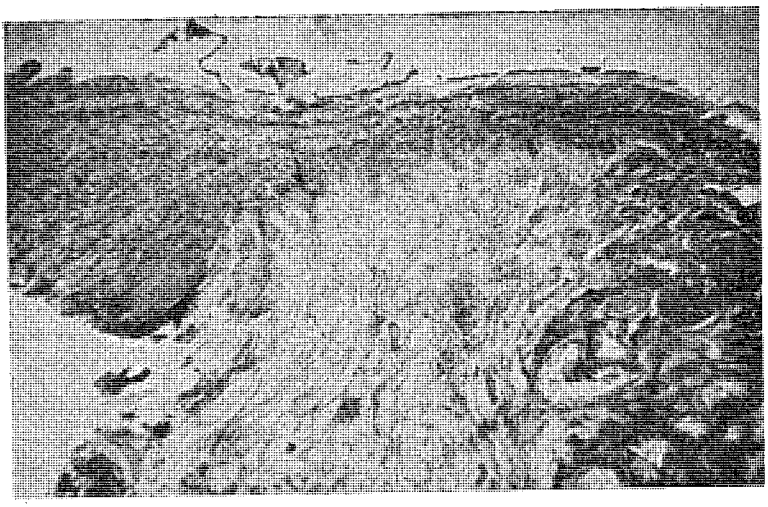

Fig. 4 — As regiões mais escuras à direita e à esquerda representam acumulos de cel. de Leydig. A área mediana inferior corresponde a tubulos hialinizados.

Gônada direita: — hialinose tubular difusa, hiperplasia de células de Leydig, além de estroma de tipo ovariano.

Nas bolsas e canal inguinal, não foi encontrada qualquer estrutura lembrando trompas.

Canal diferente e epidídimo de aspecto normal.

Laparotomia exploradora: — não foi achada qualquer estrutura mülleriana intra-abdominal.

Histologia mamária — foi feita a correção cirúrgica da ginecomastia e a microscopia de ambas as glandulas revelou tecido mámario com desenvolvimento tubular.

Uretroscopia e cistoscopia: — uretra e bexiga normais.

Cariotipo: — sangue periférico, cultura de leucocitos (10) padrão 44 XX (fig. 8).

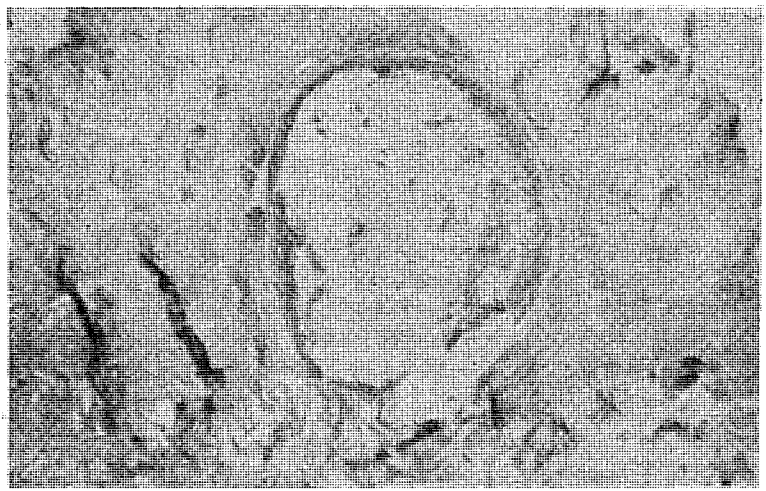

Fig. 5 — Folículo de Graaf.

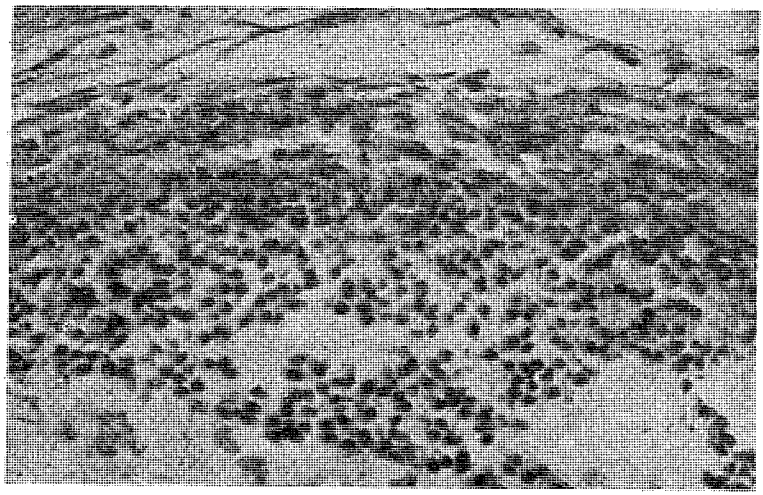

Fig. 6 — Corpúsculos de Call-Exner.

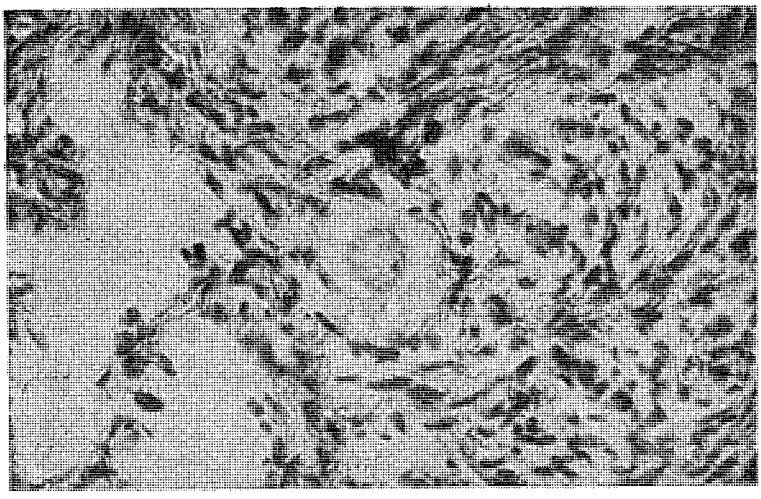

Fig. 7 — Folículo primordial.

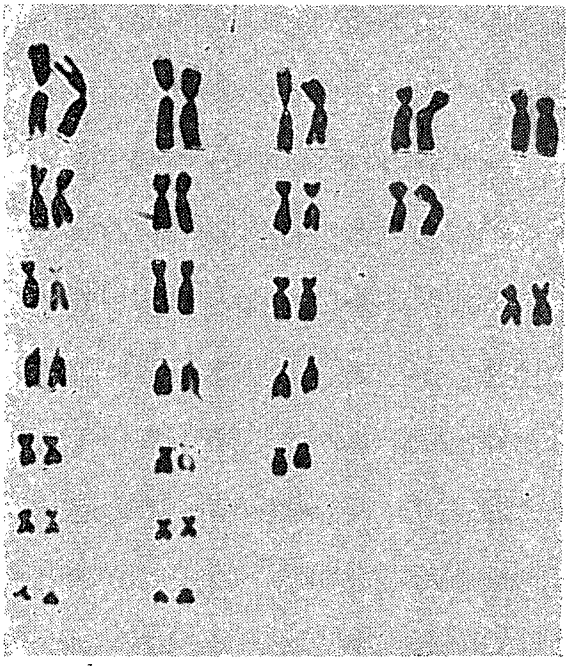

Fig. 8 — Cariotipo — 44 XX.

## *DISCUSSÃO*

Pacientes com hermafroditismo verdadeiro apresentando estrutura testicular semelhante àquela encontrada na síndrome de Klinefelter têm sido relatados. Alguns apresentavam, entretanto, características clínicas que permitiam diferenciá-los desta síndrome. Os casos de Bernardinelli (1), Armstrong (2), Gordon e cols. (3), Ferguson-Smith e cols. (4), Clayton e cols. (5) e Bunge e Bradbury (6), apresentam mal formação de genitália externa.

Hungerfordt e cols. (7) relatam um caso sem anomalia de genitália externa, mas com estrutura müllerianas abdominais presentes.

O caso aqui relatado assemelha-se à síndrome de Klinefelter em vários aspectos, tais como o fenotipo masculino, genitália externa e interna masculinas normais, gônadas firmes e pequenas e a ausência de estruturas müllerianas. Também alguns dados complementares são semelhantes, como a histologia testicular, a elevação das gonadotrofinas urinárias e a cromatina nuclear positiva.

Sempre que determinada a cromatina nuclear foi positiva (5-8) e o cariotipo de padrão 44a + XX (11, 7, 9), o que também ocorreu em nosso paciente. O hermafroditismo foi de tipo alternante (1, 3, 4) ou, como no presente caso, unilateral (2, 5-7).

É possível que outros casos semelhantes a este tenham ocorrido nos quais a biópsia gonadal e a investigação cromossômica tenham sido dispensadas devida à evidência clínica de Síndrome de Klinefelter.


### RESUMO

É estudado um hemafrodita verdadeiro com fenótipo masculino, gônadas nas bolsas com tecido ovariano e testicular na bolsa esquerda. sem hipospadia e com ginecomastia. A laparotomia não evidenciou qualquer estrutura mulleriana. A histologia gonadal revelou hialinose tubular e hiperplasia difusa das células de Leydig. À esquerda foi encontrado um folículo de Graaf e um folículo primordial. A cromatina foi positiva e o cariotipo 44 + XX.

SUMMARY

A case is presented of a true hermaphrodite whith male phenotype, gonads in the scrotum with ovarian and testicular tissue in the left g onad, without hypospadias and with gynecomastia. Laparetomy showed no evidence of Müllerian structures. Gonadal histology showed tubular hyalinosis and Leydig cell hyperplasia. On the left a primordial and Graaphian folicles were found. The sex chromatin pattern was positive and the idiogram presented 44A — XX.

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# NOTICIÁRIO

## VII CONGRESSO BRASILEIRO DE ENDOCRINOLOGIA E METABOLOGIA

13 à 16 de Agôsto de 1968

I — Local: Grande Hotel do Recife

II — Comissões do Congresso:

a) Comissão Executiva:
Presidente: Nelson Chaves
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b) Comissão Científica:
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c) Comissão de Finanças:
Presidente: José Antonio Aamaral
Weydson Leal
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Enilde Guimarães
Roberto Azevedo

e) Comissão Social:
Ney Cavalcante: Presidente
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Sonia Calixto
Eleta Portela
Elza Freitas
Publicidade e Publicações:
Emmanuel Teixeira: Presidente
Eduardo Maranhão
Hermann Voss
José Otávio Cavalcante

## VIII CONGRESSO BRASILEIRO DE ENDOCRINOLOGIA E METABOLOGIA

13-8-68

21.00 h. Abertura Solene
Conferência: "Regulação Neurohumoral da Adeno Hipofise"

14-8-68 *Simpósio sôbre Suprarenais.*

09.00 h. Metabolismo e transporte dos hormonios corticais.
09.15 h. Contribuição do Laboratório no Diagnóstico das Doenças Cortico — Adrenais.
09.30 h. Aspectos atuais da terapeutica da Sindrome de Cushing.
09.45 h. Hiperaldosteronismo primário.
10.00 h. Sindrome Adreno — Genital. Conduta Diagnostica.
10.15 h. Intervalo.
10.30 h. Discussão.
11.10 h. Conferência sôbre Diabetes.

Tarde: 15.00 h. Conferência: "Regulação da Secreção de Tireocalcitonina"

18.00 h. Temas Livres.

15-8-68 *Simpósio sôbre Gonadas.*

09.00 h. Determinação Genética do Sexo.
09.15 h. Conduta atual no Diagnóstico dos estados intersexuais.
09.30 h. Sindrome de Feminização Testicular.
09.45 h. Hipogonadismo masculino.
10.00 h. Conduta atual no tratamento das Criptorquídias.
11.10 h. Conferência sôbre: "Hemorragias Disfuncionais"
10.15 h. Intervalo.
10.30 h. Discussão.

Tarde: 15.00 h. Conferência sôbre: "Patologia Hipofisaria".
18.00 h. Temas Livres.
20.00 h. Mesa Redonda: "O Ensino da Endocrinologia no Curriculo Médico".

16-8-68

*Simpósio sôbre Tireoide*

09.00 h. Cinética do Iôdo.
09.15 h. Disormonogenese Tireoideana.
09.30 h. Aspectos imunopatogenicos nas tireopatias.

16-8-68

09.45 h. Conceito atual da etiopatogenia da D. de Basedow.
10.00 h. Conduta terapêutica no bócio nodular atóxico.
10.15 h. Intervalo.
10.30 h. Discussão.
11.10 h. Conferência sôbre: "Bócio Endêmico".

Tarde: 15.00 h. Conferência sôbre: "Osteopatias endocrino metabolicas".
18.00 h. Temas Livres.

Noite: Jantar de Encerramento.

NOTA: Taxa de inscrição: NCr$ 50,00 e NCr$ 20,00 por acompanhante. Os resumos dos trabalhos deverão ser encaminhados até o dia 15 de julho.
Endereço oficial do Congresso, para correspondência:
Dr. Fernando Almeida
Av. Conde da Boa Vista 1640, Recife-Pe.

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