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Diabetes in Bearded Women (Achard-Thiers-Syndrome)

A Clinical and Metabolic Study of 20 Cases

Par

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Summary. Twenty patients, selected on the basis of simultaneous existence of overt diabetes and marked hirsutism, were submitted to clinical and biological investigations. Obesity, hypertension and angiopathy were present in most of these patients. Metabolic investigations afforded valuable proof of hypercorticism associated with depressed activity of insulin. Nevertheless, increased steroiduria was also observed in groups of non-hirsute diabetic women carefully paired for age. Thus the Achard-Thiers syndrome cannot be separated with certainty from common overt diabetes.

Résumé. Vingt cas de syndrome d'Achard-Thiers sont soumis à une étude clinique et à des investigations biologiques. Dans la majorité des cas, le diabète, tardif et non acidosique, et l'hirsutisme sont associés à de l'obésité, de l'hypertension artérielle et une artériopathie diabétique. Les explorations métaboliques mettent en évidence un hypercorticisme conditionnant la réduction de sensibilité à l'insuline. La stéroïdurie accrue de ces patientes se retrouve cependant dans des groupes témoins de patientes diabétiques non hirsutes. Les auteurs pensent que le syndrome d'Achard-Thiers, défini comme le diabète des femmes à barbe, ne peut donc être formellement dissocié du diabète gras commun.

Zusammenfassung. Bei zwanzig Frauen mit Achard-Thiers-Syndrom wurden klinische und biologische Untersuchungen durchgeführt. In der Mehrzahl der Fälle handelte es sich um eine Kombination von Altersdiabetes und Hirsutismus mit Fettsucht, Hypertonie und diabetischen Gefäßerkrankungen. Die Stoffwechseluntersuchungen deuten auf einen Hypercorticismus als Ursache einer herabgesetzten Insulinempfindlichkeit hin. Die erhöhte Steroidausscheidung, die bei diesen Patienten gefunden wurde, konnte jedoch auch bei anderen diabetischen Frauen ohne Hirsutismus beobachtet werden. Nach Ansicht der Autoren kann das Achard-Thiers-Syndrom, der Diabetes der bärtigen Frau, nicht formal vom üblichen Altersdiabetes mit Fettsucht abgegrenzt werden.

In 1921 Achard and Thiers reported the first observation of co-existing hirsutism and diabetes, and related this syndrome to the hyperplasia of the adrenal cortex, detected at autopsy[1]. In the later described Cushing's and Conn's syndromes, the clinical features are definitely correlated with the abnormal function of the adrenal cortex, so much so that biological proof of this anomaly is a prerequisite for the clinical diagnosis. In contradistinction, the significance of the Achard-Thiers syndrome remains a matter of debate[3]. As a nosological entity, it has been either ignored[34] or considered under various and ambiguous denominations: diabetes of the late adrenogenital syndrome[5] or dissociated form of chronic hypercorticism[17,20]. It is the aim of the present paper, based on a study of 20 documented cases, to point out the clinical and biological signs of hypercorticism, to evaluate the characteristics of the coexisting diabetes and, on the basis of these data, to delineate the syndrome in regard to other syndromes of hypercorticism and to common diabetes.

Patients studied and methods

1. The 20 patients studied were selected on the basis of the simultaneous existence of overt diabetes and marked hirsutism. The diabetic condition was tested by fasting glycemia and oral glucose tolerance test.

2. Blood glucose was measured according to Hoffman[22], with the Technicon Autoanalyzer. The values indicated in the tables are the mean results of several estimations.

3. The intravenous glucose tolerance test was carried out according to Conard et al.[10] and Conard[9]. It is based on blood sugar determinations every 10 minutes for 60 minutes, after rapid intravenous injection of 0.33 g glucose/kg. During this period the blood glucose level falls exponentially. The glucose assimilation coefficient is calculated as the slope(K) of the straight line plot of the logarithm of blood sugar against time (t). $K = \frac{log_{10} C_1 - log_{10} C_2}{t_2 - t_1} \times log_n 10$. It indicates the basic rate of glucose assimilation by the tissues[19].

4. The hypoglycemic effect of insulin was studied by the analytical procedure described by Franckson[18]. After rapid intravenous injection of 0.1 U/kg the fall in blood sugar is the resultant of two opposing processes: the increased uptake by tissues and a more or less decreased release of hepatic glucose. Mathematical analysis of the decrease in the blood sugar (C) with respect to time (t) yields two factors: one that represents the slope of the exponential utilization rate induced by insulin (i), and another that expresses the quantity of glucose that is still secreted by the liver into the blood (a); the relation between these two processes is given by the equation

$$C = be^{-it} + at$$

The values of *i* and *a* given in the tables are the mean results of at least two tests.

5. Urinary 17-ketosteroids were measured after chlorhydric hydrolysis, ether extraction and purification by the method of CAHEN and SALTER, as modified by JAYLE[23]. The Zimmermann colorimetric assay was performed according to the technique of CALLOW[8]. Figures given for basic excretion are the result of at least three consecutive estimations.

6. Urinary 17-hydroxysteroids were measured by the technique of REDDY et al.[29], in a limited number of cases.

7. Chromatography of 17-ketosteroids was carried out in 12 cases using the technique of DINGEMANSE and HUIS IN'T VELD[14, 15].

8. Cortisol production rate was estimated in 3 cases using a method derived from COPE and BLACK[11] and described by COPINSCHI, CORNIL and FRANCKSON[12].

9. The clinical data are expressed as the mean and standard deviation. For group comparison, the results of the biological investigation are expressed as the mean $\pm$ S.E.M.

Clinical data

1. The mean age of this series was 65 years, ranging from 46 to 83 (Table 1).

2. Diabetes had never been apparent before the age of 40; at the time of observation its mean duration was 9 (0—20) years. This maturity-onset diabetes was characterized by the absence of ketoacidosis and by low insulin requirements which never exceeded 30 U, with a mean of 12 U/day (Table 1).

The fasting blood glucose was 175 $\pm$ 45 mg/100 ml. Pathological values were obtained in all cases, in fasting as well as after oral glucose administration. In most cases the classical vascular complications of diabetes were present (Table 1). The cholesterol level was moderately elevated: 285 $\pm$ 90 mg/100 ml. The values for total lipids were high: 1100 $\pm$ 300 mg/100 ml. Serum proteins were of normal values and electrophoresis detected only minor increases in the percentage of α_2-globulin (13.1 $\pm$ 3.9%).

In more than a quarter of the cases a familial history of diabetes was recorded. Three patients had babies of 4 kg or more (Table 2).

3. *Hirsutism.* Abnormal hair growth on the face represented the major sign, accompanied in some cases by other signs of virilism: increase of body hair growth, baldness, and hoarseness. In these cases, hirsutism appeared after menopause and except for three women who had large infants, the past gynecological history was negative.

On the other hand, 4 cases gave a history of primary amenorrhea with sterility or secondary amenorrhea; hirsutism appeared early in life and was accompanied by signs of definite masculinization: hypertrophy of the clitoris, android development of musculature and hyperplasia the breast.

4. Obesity was noted in 18 of the 20 patients, either in the past (4 cases) or at the time of observation (14 cases). The maximal weight reached by each patient was 164 $\pm$ 22% of the theoretical weight calculated from the Vandervael formula[33].

5. Fifteen out of the 20 patients had or had had markedly high blood pressure. At the time of obser-

Table 1. *Clinical and metabolic characteristics of the diabetes*

Case	Age at admission	Age at onset of diabetes	Therapy at admission	Carbohydrate metabolism G_0 mg%	Carbohydrate metabolism G_{120} mg%	Lipid metabolism Cholest. mg%	Lipid metabolism total lipid	Protein metabolism total mg%	Protein metabolism Alb. %	Protein metabolism α_2-Glob. %	Nephropathy	Retinopathy	Arteritis
1 L.L.	52	42	D.	165		296	1540	5.70	43.4	20.3	++	++	—
2 V.S.	50	41	D. + H.D.	175		369	1320				—	—	—
3 V.A.	65	45	D. + H.D.	200		441	1470	6.00	64.0	13.8	—	+++	—
4 B.E.	72	62	D. + I (15)	215		328					+	+++	+
5 V.L.	60	60	D.	150		438		7.42	59.8		—	CAT.	—
6 D.M.	83	78	D. + I (10)	145	242	304		8.72	52.2	10.4	++	+++	+
7 D.B.	78	61	D. + I (30)	215		223						+	
8 V.H.	59	48	D. + I (15)	145		220							
9 D.M.	80	63	D. + I (15)	215		225					—	+	—
10 L.H.	64	60	D. + I (20)	185	218	175		8.20	52.3	6.4	+	—	—
11 R.M.	80	80	D.	210	307	144		6.70	51.3	12.3	—	CAT.	—
12 P.S.	78	59	D. + I (30)	110		210					—	+	+
13 V.R.	53	50	D.	255	374	249		6.51	48.0	10.1	++	+++	—
14 S.J.	57	50	D. + I (30)	215		263					+++	+	+
15 E.A.	71	59	D. + I (30)	200	355	305	1220	8.20	41.9	13.5	+	—	+
16 A.H.	64	45	D. + I (15)	135	282	282	900	7.00	46.2	13.0	—	++	+
17 M.G.	73	73	D. + I (15)	165		336	885	8.10	36.9	17.2	+++	—	—
18 P.A.	46	46	D.	135		286	1150				—	++	—
19 G.H.	46	46	D.	140	319	261	660	7.20	50.1	11.1	—	—	—
20 S.M.	71	70	D.	105	246	325	900	8.20	52.6	15.8	—	—	—

Therapy: D. = diet; H.D. = oral hypoglycemic drugs; I = insulin (units/day)
Blood glucose: G_0 = fasting; G_{120} = 120th minute of O.G.T.T.
Nephropathy (blood urea > 50 mg/100 ml; urea clearance > 60% of normal; proteinuria)
Retinopathy (stage: +, ++, +++; CAT. = cataract).

Table 2. *Clinical characteristics*

Case	Age	Weight (kg) admission	Max. Weight in past	Obesity	Blood Pressure		Hyper-tension	Diabetic Heredity	Pregnancies		Menopause
					Present	Maximum in past			No.	Birth W. Kg	
1 L.L.	52	82		+	165— 90	260	+	—	2	3.5—5	50
2 V.S.	50	84	103	+	120— 80	normal	—	+	1	3.5	45
3 V.A.	65	57	75	(+)	220—100		+	—	1	3.5	30
4 B.E.	72	63		+	220—100		+	—	4	3.5	
5 V.L.	60	99	110	+	200—140	230	+	—	2	5.0	50
6 D.M.	83	74	100	+	190—110		+	—	10	4.0	39
7 D.B.	78	87	100	+	140— 80	normal	—		6	normal	
8 V.M.	59	81	125	(+)	180—100		+		0		
9 D.M.	80	70		+	190—110		+		6	normal	
10 L.M.	64	87	91	+	250—115	260	+	—	1	3.5	53
11 R.M.	80	59			190—100	200	+		13		50
12 P.S.	78	62	92	+	200— 90		+	+	3	normal	52
13 V.R.	53	50	59	—	160—100	270	+	—	0	sterility	primary amenorrhea
14 S.J.	57	84		(+)	175—120	200	+		1	3.5	45
15 E.A.	71	54	84	(+)	165—105	170	+	+	12	normal	56
16 A.H.	64	86		+	140— 80	210	(+)	+	2		spaniomen. 49
17 M.G.	73	69		+	160—100		+	—	12		56
18 P.A.	46	85		+	155—100		+		2	normal	
19 G.H.	46	93	113	+	150— 90		—	+	1	3.1	spaniomen.
20 S.M.	71	110	120	+	165—100	170	+	—	1	3.5	52

Obesity and hypertension: + = actual; (+) = past.

vation, the mean values for blood pressure were 180/110 (Table 2).

6. It should be stressed that in none of the cases studied were there striae, muscular atrophy, or radiological signs of osteoporosis.

Biological investigations

1. The intravenous glucose tolerance test yielded a glucose assimilation coefficient (K) with the mean value of 0.56 ± 0.07, ranging from 0.2 to 1.4 (Table 3)*. In the normal population the mean value of K decreases from 1.6 to 0.7 between 46 and 83 years[4], the age limits of the present study.

2. The intravenous insulin test was carried out in 16 cases. The results (Table 3) show that, contrary to what is observed in the normal subject, insulin had only a small effect on the hepatic glucose release during the hypoglycemic stage: the factor (a) which is an estimate of the residual glucose output was generally important and averaged 1.75 ± 0.3 mg/min/100 ml blood. This value is of the same magnitude as that observed in common diabetes[18].

The increased rate of glucose utilization induced by insulin, as expressed by the factor i, has a mean value of 3.20 ± 0.53. In the nondiabetic population the mean value of this index changes from 7.5 to 5.9 between 45 an 85 years[4]. It is thus markedly depressed in the cases studied, indicating a reduction of the hypoglycemic action of exogenous insulin.

* In order to facilitate the presentation of data, the factor 10^{-2} included in the value of K and i has been systematically omitted in text and tables.

Table 3. *Biological investigations*

Case	K*	a	i*	17-K S mg/24 h	17-OHS mg/24 h	Cortisol mg/24 h
1 L.L.	0.3			8.3		
2 V.S.	0.5	2.0	10.0	7.8	14.3	
3 V.A.	1.4	2.2	3.2	13.5		
4 B.E.	0.3	0.0	1.4	13.4		
5 V.L.	0.5	0.7	3.6	11.7		
6 D.M.	0.5	0.3	2.4	5.5		
7 D.B.	0.5	1.4	1.8	14.1		
8 V.H.	0.7	0.6	1.9	33.7		
9 D.M.	—	0.7	1.6	12.3		
10 L.H.	0.6	1.0	2.2	14.0		
11 R.M.	0.5	1.6	2.5	6.3		
12 P.S.	0.6	1.2	2.4	8.0		
13 V.R.		3.5	4.6	7.0		
14 S.J.	0.2			10.1		
15 E.A.	0.5	1.0	5.5	7.7	8.4	
16 A.H.	0.4	0.7	3.0	8.9	11.9	22.3
17 M.G.	0.4			9.0	5.0	
18 P.A.	0.5			9.7	14.3	
19 G.H.	0.5	0.1	2.4	21.0	11.4	26.5
20 S.M.	1.1	0.2	2.9	15.8	10.9	25.4

* Factor 10^{-2} has been omitted.

K = glucose assimilation coefficient;
a = residual hepatic glucose output (mg/min/100 ml);
i = insulin activity index.
Urinary 17 K.S. and 17 OH. Cortisol production rate.

3. The excretion of 17-KS had a mean value of 11.9 ± 1.45 mg/24 hr. In 15 out of the 20 cases this level was above the upper limit of the normal for the age of the patients (Fig. 1).

As controls, 24 hr urinary excretion of 17-ketosteroids was measured in 20 normal women, paired for age with the present Achard-Thiers cases (data selected from BASTENIE and FRANCKSON, 1955)[5]. In these con-

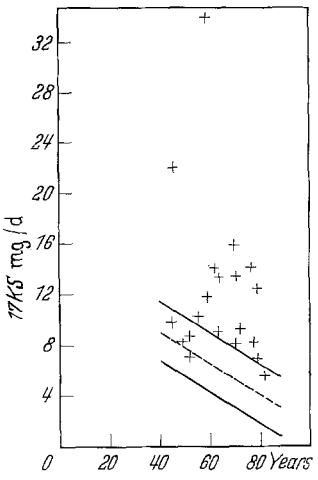

Fig. 1

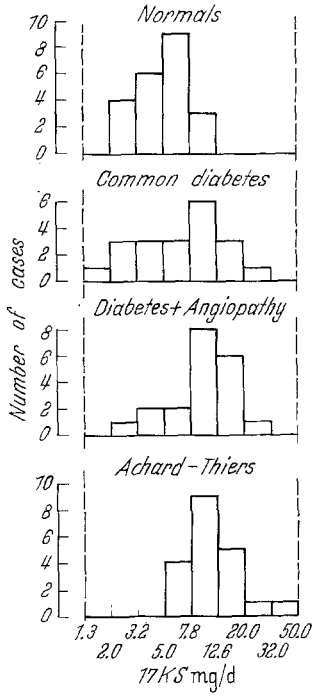

Fig. 2

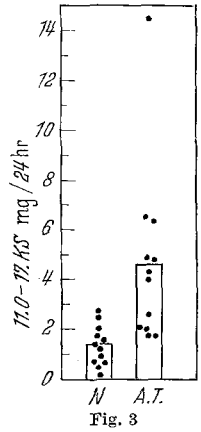

Fig. 3

trols the mean excretion was 5.7 ± 0.46 mg/24 hr. The difference between the groups is highly significant ($t = 3.931$; $df = 38$; $P < 0.001$).

The values observed also tend to be higher than those observed in women, also paired for age, that had diabetes but without hirsutism or vascular disease (Fig. 2). Finally, the values were of the same magnitude as those observed in women of the same age, that had common diabetes and vascular lesions. In these patients the daily excretion was 11.4 ± 1.26 mg/24 hr (BASTENIE et al., 1958)[6].

4. Excretion of 17-hydroxysteroids was above normal in 6 out of 7 patients studied (Table 3).

5. Chromatography of the urinary 17-ketosteroids has been carried out for 12 patients. The mean values obtained were within the normal range according to both DINGEMANSE et al.[15] and our standards[5], except for 11-oxy-ketosteroids (fractions VI and VII = 4.63 ± 1.01 mg/24 hr) which were significantly increased ($t = 3.100$; $df = 11$; $P < 0.02$) when compared (Fig. 3) with values obtained in 12 control cases of the same age (1.41 ± 0.23 mg/24 hr).

6. In 3 recently studied cases the cortisol production rate has been estimated. The values obtained (22.3; 26.5; 25.4) exceeded the upper limit of normal, but were lower than the mean values observed by COPINSCHY et al.[13] for young obese patients (31. 3 ± 3. 6 mg/24 hr).

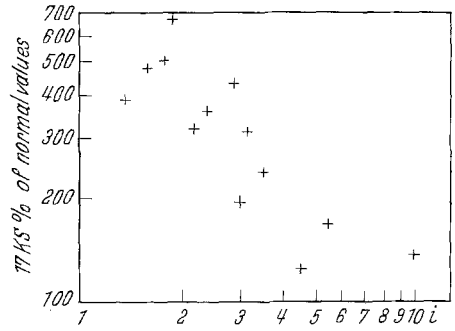

Fig. 4. Correlation between urine 17-KS (expressed in per cent of normal values for age and ranged on a logarithmic scale) and insulin activity index i, (also on a logarithmic scale)

7. Between the urinary 17-ketosteroids, expressed as per cent of normal values for age[21], and the index of insulin activity i, there was an inverse relationship (Fig. 4), which is statistically highly significant ($r = 0.795$ for $df = 14$; $P < 0.001$).

Fig. 1. Values of the urinary 17-K.S. (mg/24 hr) plotted against the age of the patients. Mean normal value and limits of normal values (95% confidence limits) in women, in relation with age, according to BASTENIE and FRANCKSON[5] are presented

Fig. 2. Distribution of the 17-K.S. excretion (mg/24 hr) in several selected populations. In each group the values are those observed in 20 women, paired for age with the Achard-Thiers cases. The values of the 17-K.S. are ranged on a logarithmic scale

Fig. 3. Chromatographic fraction of urinary 11-oxy-17-ketosteroids (mg/24 hr) in 12 cases of Achard-Thiers Syndrome and in 12 controls of the same age

Case reports

1. Case No. 16, A. H. (St. P. Hosp. 34, 868)

At the age of 25 this patient had noticed the onset of facial hypertrichosis, masculine growth of body hair and menstrual irregularities. At the age of 48 diabetes was discovered. A diagnosis of hypercorticism was made, based upon "muscular development, virilism, 17-KS excretion of 25 mg/day, without osteoporosis or striae". The pituitary region was submitted to x-ray therapy.

On admission (Fig. 5) the patient was 63 years old. Her diabetes was treated with diet and insulin, 10 to 20 U/day. She was obese (86 kg/163 cm), hirsute, hypertensive (160—210/100—110 mm Hg) and had important cerebral and peripheral vascular changes. The E.C.G. showed sequelae of a posterior myocardial infarction and calcification was visible along the arteries of both legs. One toe had been amputated. The fundus showed diabetic retinopathy stage II. Blood cholesterol was 280 mg/100 ml and total lipids 900 mg/100 ml.

The fasting blood glucose was 135 mg/100 ml; $K = 0.4$; factor $a = 0.7$ and index $i = 3.0$. A test for insulin sensitivity according to FRANCKSON[18] indicated low glucose uptake, which was but slightly increased when insulin was simultaneously injected at 30 to 300 mU/kg ($K_0 = 0.4$; K_i (30) = 0.5; K_i (300) = 1.5).

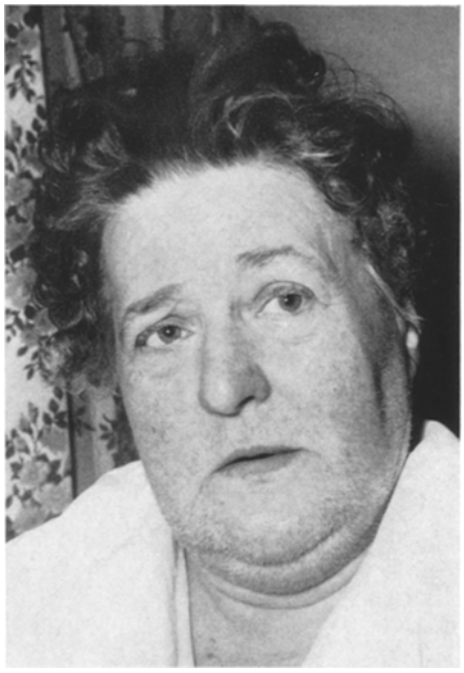

Fig. 5. Case No. 16 A. H., 63-year-old patient with Achard-Thiers-Syndrome

The 17-hydroxysteroid excretion was high: 10.2 and 13.5 mg/24 hr, that of the 17-ketosteroids had a mean value of 8.9 mg/24 hr, which was 189% of the normal value (4.5 mg/24 hr) for the age of this patient.

2. Case No. 15, E. A. (St. P. Hosp. 61, 624)

This patient, aged 71 at the time of admission, daughter of a diabetic, had been obese (84 kg/155 cm) and diabetic for 12 years. Insulin (10 to 20 U/day) had been given, principally because the patient neglected her diet. The patient had menstruated normally up to the age of 56 and had had 12 children, all of normal birth weight. Since menopause, facial hirsutism had developed.

On admission, the weight was normal (54 kg); moderate hypertension was observed together with arteritis in both legs. Auricular fibrillation and posterolateral myocardial alterations were seen in the E.C.G. The blood urea was 47 mg/100 ml. The urea clearance was 53% of normal; cholesterol (305 mg/100 ml) and total lipids (1200 mg/100 ml) were increased. There was no proteinuria and the eye grounds showed only moderate vascular sclerosis.

The blood glucose ranged from 160 to 240 mg/100 ml. The glucose assimilation coefficient K was 0.5; the residual hepatic glucose output $a = 1.0$, and the insulin activity index $i = 5.5$.

Urinary 17-ketosteroids amounted to 7.7 mg/24 hr, and the 17-hydroxysteroids to 8.4 mg/24 hr, which were high values for the age of the patient.

Comments

If in these patients, presenting both hirsutism and diabetes, a syndrome of overactivity of the corticoadrenal is to be implicated, such a demonstration should rely on the evolution of signs and symptoms, on the clinical data and on the results of the biological investigations.

1. Anamnestic data

The two detailed case reports illustrate the variable development of the syndrome. In the history of the first case, virilism was the presenting feature: in this young adult definite masculinization appeared, similar to that seen in the late adrenogenital syndrome. Much later in life diabetes appeared, inducing important vascular degenerative changes. The sequence of virilism appearing before menopause and late onset of diabetes, was seen in only four cases.

In the majority of the patients, the course was similar to that described in the second case report: there were no genital abnormalities and no hirsutism until after menopause, when abnormal hair growth appeared as an epiphenomenon superimposed on an apparently ordinary maturity-onset diabetes. It should be further noted that in one-third of the cases a family history of diabetes or a personal history of large babies indicated the existence of an hereditary diabetic factor. This frequency is the same as that observed in the female diabetic population at large[28].

2. Clinical data

Notwithstanding their variable evolution, on clinical examination these cases fall into one homogeneous group.

Apart from hirsutism, the constant features of the clinical picture are: obesity, hypertension, and marked angiopathy. Finally, the diabetes itself is always of late onset and characterized by the absence of ketoacidosis and low insulin requirements. If these features are consistent with the hypothesis of some form of chronic hypercorticism[17, 20, 26], it should be stressed at once, that the syndrome stays in sharp contrast to that of Cushing's, by the absence of osteoporosis, striae, asthenia and other signs of increased nitrogen catabolism.

3. Biological investigations

In these female patients, mostly beyond menopause, the exaggerated 17-KS excretion affords a valuable proof of hypercorticism. Moreover, in 6 out of 7 cases studied, the 17-OH-steroids were excreted in abnormally high quantities. In 12 patients studied, chromatography of the 17-KS indicated a high proportion of metabolites of 11-oxy-steroids (Fig. 3) exceeding the normal mean in all the cases and in significant excess in 7 cases. Finally, the 3 patients examined for

that purpose showed an increased rate of production cortisol.

Fig. 4 illustrates the inverse relationship between the excretion of 17-KS (expressed as per cent of normal) and the value of *i*, the index of the hypoglycemic activity of insulin. A similar relationship has been observed by FRANCKSON[18] in a group of 60 subjects, comprising 20 patients with corticoadrenal insufficiency, 20 normal subjects, and 20 subjects submitted to large doses of cortisone. It is indicative of the inhibited activity of exogenous (and probably of endogenous) insulin in the presence of increased amounts of glucosteroids, the metabolites of which were in the present cases largely 17-ketosteroids.

Finally, it should be remembered that in several cases of diabetes in bearded women, hyperplasia[1] or a tumor[7, 16, 32] of the adrenal has been discovered. In case No. 18 previously reported[3], removal of a hyperplastic adrenal with large adenomas was followed by a transient cure of the diabetes.

4. Conclusions

Thus there seems little doubt that in these bearded diabetic women hypercorticism is the origin of the hirsutism[2, 30] and plays a role in the diabetic condition. Nevertheless, this demonstration of hypercorticism does not permit us to separate with certainty these patients from non-hirsute diabetic women. Hypertension and obesity are found in a great number of diabetics. As shown in Fig. 2, there is marked overlapping of the values of 17-KS in the group of patients with Achard-Thiers syndrome and a group of diabetic women carefully paired for age. Moreover, if the patients with diabetes and hirsutism are compared with non-hiruste diabetic women with angiopathy, no difference can be detected in the 17-KS excretion. That hypercortism is present in the diabetic patients with angiopathy was suggested by previous work[6] and is claimed in recent publications[24]. Finally, in simple obesity an increase in the excretion of steroids and in the production of cortisol has recently been described[13, 25, 27, 31].

Although the syndrome of diabetes in bearded women is characterized by clinical and biological signs of hypercorticism, its real significance remains doubtful, especially in view of our limited knowledge of the role of the adrenal cortex in obesity or in maturity-onset diabetes and its vascular complications.

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