IMAGING FUNCTIONAL NODULES OF THE ADRENAL GLANDS WITH ^{131}I-19-IODOCHOLESTEROL

William H. Beierwaltes, Martin F. Sturman, Ung Ryo, and Rodney D. Ice

University of Michigan Medical Center, Ann Arbor, Michigan

Only in the instance of the hyperfunctioning adrenal cortical adenoma with Cushing's syndrome is the uptake of ^{131}I-19-iodocholesterol markedly decreased to absent in the adrenal cortices outside the adenoma. The mechanism for this lack of function outside the hyperfunctioning adrenal cortical adenoma presumably is suppression of pituitary ACTH by cortisol excess from the adrenal cortical adenoma resulting in subnormal stimulation of normal adrenocortical tissue. We report the occurrence of hyperactivity in one adrenal gland presumably from a functioning nodule, resulting in increased uptake with suppressed uptake of ^{131}I-19-iodocholesterol in the contralateral adrenal cortex in the absence of Cushing's syndrome. One 67-year-old woman had diabetes mellitus, a massively fatty liver, a dexamethasone nonsuppressible uptake of ^{131}I-19-iodocholesterol in her right adrenal nodule, and a normal response to ACTH stimulation of the opposite adrenal gland. A 21-year-old woman had obesity, diabetes, progressive hirsuitism, sterility, and slightly elevated urinary 17-ketosteroid excretion. The increased uptake in the hot nodule in the right adrenal was suppressible with dexamethasone and ACTH produced a normal uptake in the opposite adrenal gland. The similarity of these functional nodules in the adrenal cortices to functional nodules previously observed in the thyroid gland with ^{131}I are apparent.

We have reported the imaging with ^{131}I-19-iodocholesterol and the Anger camera of the diffusely overactive adrenal glands in patients with Cushing's syndrome due to pituitary ACTH excess (*1*), the hyperfunctioning adrenal cortical adenomas of patients with Cushing's syndrome (*2*), and the aldosterone-secreting tumors of patients with primary aldosteronism (*3–4*). Only in the instance of the hyperfunctioning adrenal cortical adenoma with Cushing's syndrome is the uptake of ^{131}I-19-iodocholesterol markedly decreased to absent in the adrenal cortices outside the adenoma. The mechanism for this lack of function outside the hyperfunctioning adrenal cortical adenoma presumably is suppression of pituitary ACTH by cortisol excess from the adrenal cortical adenoma resulting in subnormal stimulation of normal adrenocortical tissue.

We now wish to report the occurrence of hyperactivity in one adrenal gland presumably from a functioning nodule, resulting in increased ^{131}I-19-iodocholesterol uptake with suppressed uptake of ^{131}I-19-iodocholesterol in the contralateral adrenal cortex in the absence of Cushing's syndrome.

METHODS

Patients. The first patient was a woman nurse, 67 years old, when we first saw her on 6–19–72 to give her a tracer dose of ^{131}I-19-iodocholesterol to see if it would have a delayed disapperance from her fatty liver. She had had a fatty liver without cirrhosis proved by biopsies and liver function tests in 1960, 1968, and 1972. She had been obese "all her life." On her first University of Michigan Hospital admission, 5–23–72, diabetes mellitus was diagnosed for the first time. Her blood pressure was 135/85. She was 5 ft 4 in. in height and weighed 136 lb. She was also found to have Type IV hyperlipoproteinemia and arteriosclerotic heart disease with an old anteroseptal infarct and intermittent claudication. She had mild cardiomegaly and her liver was percussed as 26 cm in height, 16 cm below the right costal margin.

Received May 18, 1973; revision accepted Oct. 15, 1973.

For reprints contact: William H. Beierwaltes, Nuclear Medicine Division, University of Michigan Medical Center, Ann Arbor, Mich. 48104.

TABLE 1. ^{131}I-19-IODOCHOLESTEROL PERCENT UPTAKE AND ADRENAL CORTICAL STEROID VALUES IN FIRST PATIENT

Day	Preparation	Urinary 17-ketosteroid (mg/24 hr) (N = 4–14)*	Urinary 17 OHCS (mg/24 hr) (N = 5–10)†	Plasma cortisol (μg/100 ml) (N = 5–20)‡	% uptake Left	% uptake Right
6–19–72	None ^{131}I-19-iodocholesterol 2.1 mCi					
6–26–72					0.0	0.10
7–01–72					0.0	0.08
	Suppression					
7–31–72		6.8	5.0			
8–01–72 thru 8–17–72	Dexamethasone 0.5 mg q 6 hr daily					
8–04–72	^{131}I-19-iodocholesterol 1.85 mCi	5.0	1.6			
8–11–72	Dexamethasone 0.5 mg q 6 hr daily					
8–15–72					0.0	0.19
8–17–72					0.0	0.13
	Corticotrophin stimulation					
12–10–72	Baseline	9.7	8.1	7.0 (am) 7.0 (pm)		
12–11–72	Baseline	5.4	4.6	10.0 (am) 6.0 (pm)		
12–12–72	ACTH gel I.m. 80 μ	11.8	20.5			
12–13–72	80 μ					
12–14–72	^{131}I-19-iodocholesterol 2 mCi	43.5	64.5			
12–15–72 and 12–17–72	Zn-corticotrophin I.m. 40 μ					
	40 μ					
12–19–72	Zn corticotrophin I.m. 80 μ	18.0	26.6	70.0 (pm)		
12–20–72		43.0	58.5		0.05	0.22
12–21–72					0.08	0.26
12–22–72	80 μ					
12–23–72						
12–27–72					0.09 0.0	0.25 0.17

* Zimmerman.
† Porter-Silber.
‡ Vander Vies.
(*Acta Endocrinol* 38: 399, 1961).

The spleen was down 3 cm. Her diabetes was controlled on 500 mg of Orinase three times a day. She had also had an aortofemoral bypass with saphenous vein grafts done bilaterally in 1959 for peripheral arterial insufficiency.

On her admission to our Clinical Research Unit on 6–19–72, her blood pressure was 130/75 with a pulse rate of 82. She did not have the features of Cushing's syndrome. The liver was enlarged, 12 cm below the right costal margin, and firm. The spleen was not palpable. There was 1+ pitting edema on her shins. Table 1 gives her ^{131}I-19-iodocholesterol percent uptake and adrenal cortical steroid values before and after dexamethasone suppression and corticotrophin stimulation. On 6–19–72 she was given an intravenous tracer dose of ^{131}I-19-iodocholesterol (2.1 mCi in 1.8 ml in 5.4 mg of iodocholesterol). Her adrenals, liver, and spleen were imaged

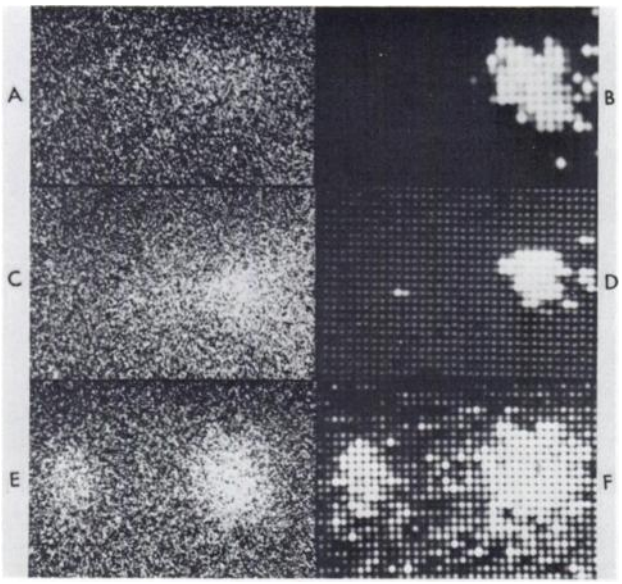

FIG. 1. Imaging of adrenals in first patient. Scintiphotos are on left and computer-altered cathode-ray display on right. (A) without treatment on 6–26–72, 7 days after tracer dose. Left adrenal does not image. Uptake was 0.0% on left and 0.10% on right. (B) After dexamethasone suppression on 8–17–72, 13 days after tracer dose and after 16 days of dexamethasone suppression. No appreciable suppression of uptake in right adrenal gland. Uptake is 0.0% of tracer on left and 0.13% on right. (C) After corticotrophin stimulation on 12–21–72, 7 days after tracer and 9 days of corticotrophin stimulation. Some uptake evident in left adrenal and increased uptake in right adrenal. Uptake was 0.08% on left and 0.26% on right.

and the percent uptake of ^{131}I-19-iodocholesterol in the adrenals was determined with our Anger scintillation camera (*5*). The scintiphoto and computer-altered cathode-ray display on 6–26–72 showed sharp imaging of the right adrenal gland (Fig. 1A) with no uptake in the left adrenal (1B). The percent uptake of the tracer dose of ^{131}I-19-iodocholesterol was 0.0% in the left adrenal and 0.10% on the right (normal difference = 0.04% ± 0.024).

These studies were repeated after dexamethasone suppression (*4*) (2 mg daily for 3 days prior to injection of radioiodinated cholosterol and continued until the completion of adrenal imaging). She was given 1.85 mCi of ^{131}I-19-iodocholesterol in 0.79 ml and 1.6 mg on 8–4–72. The bright image of the right adrenal and the lack of image of the left adrenal gland was essentially the same as before the dexamethasone (Figs. 1C and D). The percent uptake of ^{131}I-19-iodocholesterol was unsuppressed; 0.0% on the left and 0.13% on the right.

After corticotrophin stimulation on 12–21–72, 7 days after the tracer (2 mCi in 0.4 ml and 1.33 mg) and 9 days of corticotrophin stimulation, normal uptake is evident (Fig. 1E) in the left adrenal (0.08%) and an increased uptake is present in the right adrenal (Fig. 1F) (0.026%).

The steroid tests shown in Table 1 showed no definite abnormality. The plasma cortisols were usually subnormal. We have no data on the response of the ^{131}I-19-iodocholesterol uptake in normal adrenals to ACTH stimulation and so cannot say whether or not the response in the left adrenal is normal or subnormal.

The second patient was a 21-year-old lithograph clerk when her adrenals were first imaged by us for the chief complaint of hirsutism when she was referred to us for an adrenal scan in December of 1971. Her birth weight was 7 lb. In 1971 she began to experience the sudden onset of repeated episodes of depression. Recently, her weight had increased from 130 to 160 lb. In 1970, she began to have progressive hair growth requiring shaving of her face, breasts, and stomach. Her menarche occurred at age 11. Her menstrual periods were regular until 1970 when they decreased in frequency to 4–5 periods a year and she had not succeeded in becoming pregnant. On physical examination, she was 5 ft 4 in. tall and weighed 160.6 lb. Her blood pressure was 108/70–50. Her pulse rate was 78. She had mild generalized hirsutism. The uterus was small. Both ovaries were barely palpable. There were no stigmata of Cushing's syndrome. On 11–10–72, she had a clearly diabetic glucose tolerance test with a fasting blood sugar of 103 mg%. Her serum lipids and lipoprotein electrophoresis were normal. Her ^{131}I-19-iodocholesterol percent uptake and adrenal cortical steroid values before and after dexamethasone suppression and corticotrophin stimulation are presented in Table 2. They show decreased serum cortisols with normal urinary hydroxycorticoids and slightly elevated 17-ketosteroid excretion.

On 12–15–71 the patient was given an intravenous injection of 2.1 mCi of ^{131}I-19-iodocholesterol in 0.76 ml of solution in 1.6 mg of iodocholesterol base. Figures 2A and B show that she had good uptake in the right adrenal (0.09%) and subnormal uptake in the left adrenal (0.01% on 12–28–71).

After dexamethasone suppression, a repeat intravenous tracer dose of 2.09 mCi in 2.39 ml and 8 mg of iodocholesterol was given on 11–12–72. Figures 2C and 2D show complete suppression of imaging on both adrenals on 1–26–72, 8 days after the dose and 11 days on dexamethasone (from 11–9–72). On 12–14–72, she received a third dose of 2.0 mCi of ^{131}I-19-iodocholesterol in 0.4 ml of solution and $<$1.33 mg of cholesterol base. Figures 2E and F show that 9 and 14 days after the tracer and 11 and 16 days of ACTH administration the uptake in the left adrenal had increased to 0.11% and 0.08% and in the right adrenal to 0.15 and 0.28%.

TABLE 2. ^{131}I-19-IODOCHOLESTEROL PERCENT UPTAKE AND ADRENAL CORTICAL STEROID VALUES IN SECOND PATIENT

Day	Preparation	Urinary 17-ketosteroid (mg/24 hr) (N = 4–14)	Urinary 17 OHCS (mg/24 hr) (N = 5–10)	Plasma cortisol (μg/100 ml) (N = 5–20)	% uptake Left	% uptake Right
12–15–71	None ^{131}I-19-iodocholesterol 2.1 mCi					
12–21–71					0.0	0.02
12–22–71					0.07	0.12
12–28–71					0.01	0.09
11–09–72	Dexamethasone 0.5 mg q 6 hr daily					
11–12–72	Suppression ^{131}I-19-iodocholesterol 2.08 mCi					
11–15–72		15.0	7.9	4.0		
11–16–72		18.7	6.9	4.0		
11–17–72				4.0 (am) 1.0 (pm)		
11–18–72		8.0	0.3			
11–19–72		8.1	1.9	1.0 (am)		
11–20–72	Dexamethasone stopped				0.0	0.0
11–22–72					0.23	0.28
12–11–72	Stimulation Baseline			8.0 (am)		
12–12–72	ACTH gel I.m. 80 μ			3.0 (pm)		
12–13–72	ACTH gel I.m. 80 μ	43.3	34.0	10.0 (am) 40.0 (pm)		
12–14–72	^{131}I-19-iodocholesterol 2.0 mCi					
12–15–72	ZN-corticotrophin I.m. 40 μ					
12–16–72						
12–17–72	ZN-corticotrophin I.m. 40 μ					
12–19–72	ZN-corticotrophin I.m. 80 μ	31.7	31.3			
12–20–72		40.0	35.4			
12–21–72		12.0	17.0		0.07	0.14
12–22–72	80 μ	12.1	4.9			
12–23–72		15.8	10.5		0.11	0.15
12–28–72					0.08	0.28

DISCUSSION

The adrenal glands of both of these patients were abnormal as shown by adrenal imaging and percent uptake of ^{131}I-19-iodocholesterol in spite of a clinical picture and steroid values not diagnostic of an adrenocortical disease. We believe, but as yet have no venographic or surgical specimen proof, that both patients had a functional adrenocortical nodule or adenoma in the right adrenal cortex producing cortisol excess sufficient to depress uptake outside the nodule or adenoma but not associated with a classical picture of Cushing's syndrome or adrenal virilization.

Recently we have obtained a normal venogram on the younger, healthier subject. We do not feel justi-

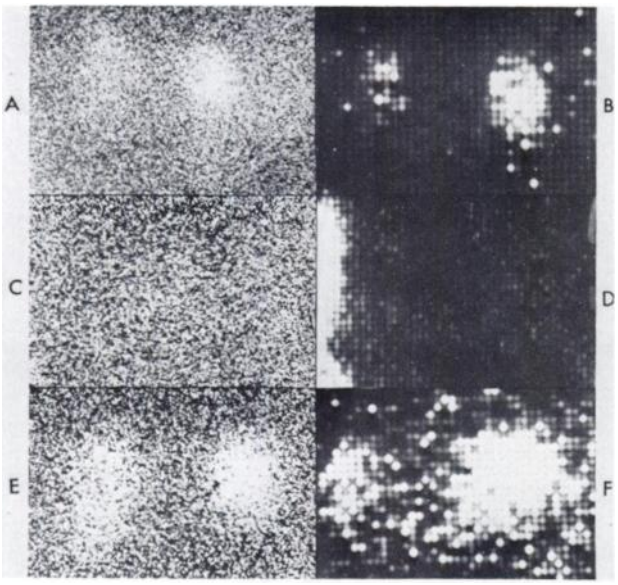

FIG. 2. Imaging of adrenals in second patient. (A) Without treatment on 12–28–71, 13 days after tracer dose of ^{131}I-19-iodocholesterol. Good uptake in right adrenal and subnormal uptake in left adrenal. Uptake was 0.01% on left and 0.09% of dose on right. (B) After dexamethasone suppression 11–20–72, 8 days after tracer and after 11 days of dexamethasone. Complete suppression of uptake in both adrenals. (C) After corticotrophin stimulation on 12–23–72 (scintiphoto) and 12–28–72 (computer display), 9 and 14 days after tracer and after 11 and 16 days of ACTH stimulation. Uptake in left adrenal was 0.11 and 0.08% of tracer and in right adrenal = 0.15 and 0.28%.

fied in removing her right adrenal surgically for study at this time. Our venogram technique has missed aldosterone tumors under 1 cm in diam and routinely under 0.5 cm in diam.

The functional adrenocortical nodule in the first patient was relatively autonomous, as shown by lack of suppression of uptake of ^{131}I-19-iodocholesterol with dexamethasone while the uptake in the functional nodule in the right adrenal of the second patient was suppressed by dexamethasone.

The strongest evidence that the cause of the picture observed here is a nodule or adenoma in the right adrenal secreting cortisol at a supernormal rate is that to date we have seen this picture previously only in patients with proved hyperfunctioning adrenal cortical adenomas associated with the classical clinical and laboratory picture of Cushing's syndrome (*2,5*). These patients had a hyperfunctioning adrenocortical adenoma in one gland proved by venography and surgery with the preponderant or total observable uptake of ^{131}I-19-iodocholesterol on that side and lack of uptake of ^{131}I-19-iodocholesterol in the contralateral adrenal, atrophic by venography. The mechanism for decreased function of the contralateral adrenal is accepted as being cortisol excess sufficient to markedly decrease ACTH stimulation of normal adrenal tissue.

Scan after ACTH. Further evidence that the cause of the picture observed here is a functional nodule or adenoma in the right adrenal is that our imaging and percent uptake values in this condition are almost identical to our findings with Na^{131}I in functional nodules of the thyroid gland without thyrotoxicosis. It is common to find radioactively "hot" nodules in the thyroid gland which may or may not be suppressible with the administration of thyroid hormone and which may produce sufficient thyroid hormone to decrease TSH stimulation of uptake of ^{131}I outside the radioactively "hot" nodule.

It is much more difficult to image the radioactively "hot" area in the adrenal gland discretely as a nodule or adenoma than it is to image functional nodules or adenomas in the thyroid gland because the adrenal glands are smaller than the thyroid, their nodules are usually smaller, the adrenals are more distant from the detector, and the percent uptake of ^{131}I-19-iodocholesterol in the adrenal gland is somewhat less than the uptake by the thyroid gland of ^{131}I from Na^{131}I. It is not unexpected that functional thyroid nodules would have been discovered before functional adrenal nodules since there are many more opportunities at present to scan the thyroid gland because the patient's thyroid gland is easily visible and palpable when it enlarges, most diseases of the thyroid gland are associated with goiter, and Na^{131}I is readily available in most hospitals.

Patients with "hot" nodules in the thyroid gland that produce sufficient thyroid hormone not only to suppress TSH stimulation of uptake in normal thyroid tissue but also sufficient to raise the serum level of thyroid hormone to levels diagnostic of thyrotoxicosis are said to have Plummer's syndrome (*6*). This syndrome in the thyroid gland is the equivalent to Cushing's syndrome in the adrenal gland associated with a hyperfunctioning adrenocortical adenoma producing cortisol excess sufficient to raise serum concentration to levels associated with Cushing's syndrome.

It is of interest, in this regard, that Plummer's disease is rare before 30 years of age (*7,8*) and the nodules are usually >3–4 cm or they are multiple before hyperthyroidism is diagnosed (*8*). The peak incidence of hyperfunctioning adrenal cortical adenomas as a cause of Cushing's syndrome, similarly, is in decades 3 and 4 (*9*).

Evidence that smaller hyperfunctioning tumors of the adrenal cortex may be present before the advent of the clinically diagnosable hyperfunctioning adrenal cortical adenoma causing the overt clinical picture of Cushing's syndrome with diagnostic hormonal values is the observation that the symptoms of Cushing's syndrome are present an average period

of 4.5 years (*10*) with a range of 1–10 years before the definitive diagnosis is made.

The smallest hyperfunctioning adrenocortical adenoma that we have imaged and removed surgically (in our first 12 patients) was 3 cm in diam. Indeed, the literature records that the average-sized adrenocortical adenoma is 100–200 gm in weight at operation (*11*).

These observations make a plausible case, therefore, for the possibility that a "Pre-Cushing's syndrome" can be diagnosed by finding a radioactively "hot" adrenal cortical nodule or adenoma with ^{131}I-19-iodocholesterol and the Anger camera with suppression of uptake in normal adrenocortical tissue in patients who are hirsute, sterile, diabetic women with or without hypertension. Although some of these women may have Stein-Leventhal's syndrome, there is increasing evidence that patients with this syndrome frequently have associated abnormalities of adrenocortical function. Indeed, two shared hormonal features of this abnormality in patients with Stein-Leventhal's syndrome and the syndrome observed in our patients are: (A) a subnormal suppression of urinary 17-KS, and (B) a somewhat excessive response of urinary 17-KS and 17-OHCS to ACTH stimulation (*12*).

Our observations obviously will raise the question of whether or not ^{131}I-19-iodocholesterol should be used fairly routinely to screen adult, hirsute, sterile, diabetic women with or without hypertension for "hot" nodules with suppression before Cushing's syndrome or Stein-Leventhal's syndrome becomes manifest.

We believe that at present it is premature to advocate the use of this technique to screen such patients for adrenal abnormality for at least three reasons:

1. We would first like to excise one of these "hot" nodules or adenomas.

2. We would like to observe an amelioration of at least some of the clinical abnormalities after excision of the source of cortisol excess.

3. The following table of radiation dose needs amplification by the addition of more radioactivity assays of human ovaries and testes after more tracer doses of ^{131}I-19-iodocholesterol since the calculations on these two organs in humans at present is based on data on only one patient each.

The radiation dose in rads/mCi of ^{131}I-19-iodocholesterol is as follows:

Whole body	1.1	Testes	0.4
Adrenals	30–40	Bowel	1.2
Liver	7–11	Sternum	0.7
Ovaries	1.7		

NOTE

Inquiries about the supply of ^{131}I-19-iodocholesterol for investigational use should be addressed to Rodney Ice, Nuclear Medicine, University Hospital, Ann Arbor, Michigan 48104.

ACKNOWLEDGMENTS

This work was supported in part by Training Grant CA 05134-11 from the U.S. Public Health Services, a grant (RR-42) from the Clinical Research Center Program of the Division of Research Resources, National Institutes of Health, in part by contract AT 11-1 2031 with the Atomic Energy Commission and by the Nuclear Medicine Research Fund.

REFERENCES

1. BEIERWALTES WH, LIEBERMAN LM, ANSARI AN, et al: Visualization of human adrenal glands in vivo by scintillation scanning. *JAMA* 216: 275–277, 1971

2. LIEBERMAN LM, BEIERWALTES WH, CONN JW, et al: Diagnosis of adrenal disease by visualization of human adrenal glands with ^{131}I-19-iodocholesterol. *N Engl J Med* 285:1387–1393, 1971

3. CONN JW, BEIERWALTES WH, LIEBERMAN LM, et al: Primary aldosteronism: Preoperative tumor visualization by scintillation scanning. *J Clin Endocrinol Metab* 33: 713–716, 1971

4. CONN JW, MORITA R, COHEN EL, et al: Primary aldosteronism: Photoscanning of tumors after administration of ^{131}I-19-iodocholesterol. *Arch Intern Med* 129: 417–425, 1972

5. MORITA R, LIEBERMAN LM, BEIERWALTES WH, et al: Percent uptake of ^{131}I radioactivity in the adrenal from radioiodinated cholesterol. *J Clin Endocrinol Metab* 34: 36–43, 1972

6. PLUMMER JS: The function of the thyroid gland containing adenomatous tissue. *Trans Assoc Am Physicians* 43: 159–164, 1928

7. THOMAS CG: Sporadic toxic goiter, surgical aspects. In *The Thyroid: A Fundamental and Clinical Text.* 3rd ed. Werner SC, Ingbar SH, eds, New York, Harper & Row, 1971, p 434

8. SILBERSTEIN GE, BURKE G, COGAN R: The natural history of the autonomous hyperfunctioning thyroid nodule. *Ann Intern Med* 67: 539–548, 1967

9. FORSHAM P: The adrenal cortex: diseases of adrenocortical hyperfunction. In *Textbook of Endocrinology.* 4th ed. Williams RH, ed, Philadelphia, WB Saunders Co, 1968, pp 339–363

10. MEYERS MA: *Diseases of Adrenal Glands.* Springfield, Ill, CC Thomas, p 35, 1963

11. MOON HD: *The Adrenal Cortex.* New York, Hoeber, Medical Div of Harper, 1961, p 227

12. KIRSCHNER MA, JACOBS JB: Combined ovarian and adrenal vein catheterization to determine site(s) of androgen overproduction in hirsute women. *J Clin Endocrinol Metab* 33: 199–209, 1971