ADRENAL CONTRIBUTION TO PLASMA OESTROGENS IN ADRENAL DISORDERS

By

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ABSTRACT

The concentrations of oestrone (Oe\textsubscript{1}) and oestradiol (Oe\textsubscript{2}) in adrenal venous and peripheral plasma (inferior vena cava, aorta and/or antecubital vein) were measured by radioimmunoassay in 8 patients in whom an adrenal disorder was suspected (group A) and 5 patients in whom an adrenal disorder was proven (group B). In group A, 6 patients had higher Oe\textsubscript{1} concentrations in adrenal than in peripheral plasma, while 5 patients had higher Oe\textsubscript{2} concentrations in adrenal venous plasma. In group B, in 3 of 4 patients with primary aldosteronism secondary to an adrenocortical adenoma, both Oe\textsubscript{1} and Oe\textsubscript{2} concentrations in the adrenal venous plasma from the side of the adenoma were greater than in peripheral plasma. A patient with Cushing’s disease showed a similar gradient for Oe\textsubscript{1} but not Oe\textsubscript{2}.

The results are consistent with the following conclusions: 1) Both Oe\textsubscript{1} and Oe\textsubscript{2} are secreted from the adrenal in neoplastic and non-neoplastic disorders in detectable but small amounts. 2) Estimates of maximal adrenal secretion rates in 3 male patients indicate that the adrenal contribution was less than 4\% (Oe\textsubscript{1}) and less than 2\% (Oe\textsubscript{2}), of reported blood production rates of oestrogens in normal men.

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Several lines of evidence suggest that there are extragonadal sources of oestrogen production. Brown et al. (1959) demonstrated that ACTH administered to women with carcinoma of the breast resulted in an increase of urinary excretion of oestrone (\(\text{Oe}_1\)), oestradiol (\(\text{Oe}_2\)) and oestriol (\(\text{Oe}_3\)) to values seen at the time of the pre-ovulatory oestrogen peak. These increments were abolished by adrenalectomy. Studies by Baird et al. (1969) revealed that \(\text{Oe}_1\), but not \(\text{Oe}_2\), concentrations in adrenal venous plasma were significantly increased after ACTH administration. Further studies by Baird & Guerra (1969) showed that \(\text{Oe}_1\) levels in peripheral plasma had a diurnal variation resembling that of cortisol. In addition to the effect of ACTH on \(\text{Oe}_1\), Saez et al. (1972) found that dexamethasone suppressed \(\text{Oe}_1\) but not \(\text{Oe}_2\) levels in peripheral plasma. These studies suggested that the adrenal is a site of \(\text{Oe}_1\) production. However, studies on peripheral conversion of androstenedione to \(\text{Oe}_1\) in both sexes suggest that most, if not all, circulating \(\text{Oe}_1\) is derived in this manner, rather than by glandular secretion (Mac Donald et al. 1967).

To determine whether the adrenal glands secrete \(\text{Oe}_1\) and \(\text{Oe}_3\), the concentrations of these hormones were determined in samples of adrenal venous plasma from 13 patients.

**MATERIALS AND METHODS**

**Patients**

Selective catheterization of the adrenal veins was performed in 13 patients as part of a diagnostic evaluation for suspected adrenal disease. In 9 patients, one adrenal vein was sampled, while in 4, samples were obtained from both adrenal veins. In all patients, the adrenal vein catheterization was performed to obtain venograms and/or adrenal venous plasma for assay in an endocrinologic evaluation. Antecubital venous samples were obtained at the time of adrenal venous catheterization in 2 patients (1 and 10, see Tables 1a and 1b). In the remaining patients, samples were obtained from the inferior vena cava (IVC). An additional sample from the aorta was obtained from patient 9. The subjects were divided into 2 groups depending upon whether an adrenal disorder was suspected (group A) or proven (group B).

**Group A (8 patients)**

Endocrine evaluation failed to establish the presence of a specific adrenal disorder in patients 1 and 2, while patients 3–8 had evidence of either 1) abnormal renin and/or aldosterone regulation, 2) Cushing’s disease, or 3) oligomenorrhea with hirsutism. Clinical data are summarized in Table 1a and presented in further detail below.

**Group B (5 patients)**

This group includes 4 patients (9–12) with primary aldosteronism secondary to an aldosterone secreting adrenocortical adenoma (Conn’s syndrome). All had arterial
hypertension and hypokalaemia in association with abnormally elevated urinary aldosterone excretion and suppressed plasma renin activity (PRA). Adrenal venography demonstrated a focal tumour which was surgically removed. Following operative removal, the clinical and laboratory abnormalities returned to normal in each patient. Patient 10 had bilateral gynaecomastia while on spironolactone therapy. After removal of the adrenal adenoma and discontinuance of the spironolactone, the gynaecomastia, hypertension and hypokalaemia regressed. The remaining patient (No. 13) had Cushing’s disease secondary to adrenal hyperplasia. Bilateral adrenalectomy was performed; adrenocortical hyperplasia was found on the left and adrenocortical atrophy on the right. Clinical data are summarized in Table 1b.

**Venography**

Adrenal venous catheterization was performed using the Seldinger technique (Seldinger 1964) under local anaesthesia and light premedication with meperidine and secobarbital. Adrenal veins were selectively catheterized; generally the right vein was entered first. Blood was collected by allowing the catheter to drain into a lightly heparinized tube. The IVC samples were obtained following sampling of the adrenal vein, without particular reference to the level of entry of the gonadal veins. The catheter was flushed with saline between samples and after injection of contrast material. In case 2, the IVC sample was from above the level of the renal veins. Blood samples were immediately centrifuged and the plasma was stored frozen until assayed.

**Hormone determinations**

Oe1 and Oe2 were quantitated by a modification of the method described previously by Kelch et al. (1973). A bovine serum albumin-absorbed sheep antiserum to 17β-oestradiol-17-succinyl-BSA (No. 704) (kindly supplied by Drs. R. Vande Wiele and I. Dyrenfurth, Columbia University) was used in an assay volume of 1.2 ml at a final dilution of 1/1 800 000. At this concentration, the antiserum bound approximately 50% of 35 pg 3H-Oe2 (S. A. 106 Ci/mmole) and 45% of 30 pg 3H-Oe1 (S. A. 106 Ci/mmole) in the absence of unlabelled oestrogens.

Cross-reactivity determinations, calculated at 50% displacement in each assay, were as follows: dehydroepiandrosterone, 0.09% (Oe1) and 0.04% (Oe2); cortisol, 0.00004% (Oe1) and 0.00003% (Oe2); and deoxycorticosterone, less than 0.012% (Oe1) and less than 0.008% (Oe2). Up to 25 μg of aldosterone showed no cross-reactivity with either Oe1 or Oe2.

Sensitivity of the assay, as determined by 95% confidence limits of counts in non-hormone containing tubes (Midgley et al. 1969) was 6 pg for Oe1 and 8 pg for Oe2. Mean blank values for 2 ml deionized distilled water were below the sensitivity of the assay for Oe1 and Oe2 and were not subtracted from values for the samples.

A male plasma pool was obtained from 3 healthy young men between 8 and 10 a.m. A female pool was obtained from 6 women, not on medications, at various stages throughout the menstrual cycle. Mean values for the male pool were 75 pg/ml (Oe1) and 35 pg/ml (Oe2). The female pool yielded mean values of 194 pg/ml and 189 pg/ml for Oe1 and Oe2 respectively. The mean inter-assay coefficient of variation for these pools was 9.0% for Oe1 and 9.7% for Oe2. Recovery of tracer 3H-Oe1 and 3H-Oe2 (approximately 1000 cpm of each isotope, S. A. 106 Ci/mmole), added to samples prior to extraction and chromatography, was 64 ± 4% and 68 ± 2% respectively. All
**Table 1a.**

Group A (suspected adrenal disorders).

Oestrone (Oe₁) and oestradiol (Oe₂) concentrations in inferior vena cava, antecubital and adrenal venous plasma (pg/ml).

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Clinical</th>
<th>Venogram</th>
<th>Oestrogen</th>
<th>Peripheral vein&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Left adrenal vein</th>
<th>Right adrenal vein</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>M</td>
<td>Essential Hypertension</td>
<td>Not performed</td>
<td>Oe₁</td>
<td>99</td>
<td>291</td>
<td>291</td>
<td>-</td>
<td>No adrenal abnormality; methyldopa; spironolactone; hydrochlorothiazide</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>M</td>
<td>Essential Hypertension</td>
<td>Hyperplasia</td>
<td>Oe₁&lt;sup&gt;α&lt;/sup&gt;</td>
<td>137</td>
<td>119</td>
<td>-</td>
<td>-</td>
<td>No adrenal abnormality</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>M</td>
<td>Hypertension</td>
<td>Normal</td>
<td>Oe₁</td>
<td>104</td>
<td>168</td>
<td>81</td>
<td>-</td>
<td>? Primary aldosteronism</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>M</td>
<td>Hypertension</td>
<td>Normal</td>
<td>Oe₁</td>
<td>136</td>
<td>893</td>
<td>109</td>
<td>-</td>
<td>Dexamethasone 2 mg/day (3 days); ? primary aldosteronism</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>F</td>
<td>? Cushing's disease</td>
<td>Normal</td>
<td>Oe₁</td>
<td>282</td>
<td>313</td>
<td>-</td>
<td>-</td>
<td>Oligomenorrhea</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>F</td>
<td>Sclerocystic ovarian disease; hirsutism</td>
<td>Normal</td>
<td>Oe₁</td>
<td>296</td>
<td>235</td>
<td>109</td>
<td>338</td>
<td>Oligomenorrhea</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>F</td>
<td>Low renin hypertension Diabetes Mellitus</td>
<td>Normal</td>
<td>Oe₁</td>
<td>96</td>
<td>376</td>
<td>-</td>
<td>-</td>
<td>Dexamethasone 2 mg/day (7 days)</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>F</td>
<td>Low renin hypertension</td>
<td>Normal</td>
<td>Oe₁</td>
<td>275</td>
<td>166</td>
<td>92</td>
<td>76</td>
<td>Right ovariectomy and hysterectomy</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patient 1 had peripheral sample from the antecubital vein, all others in this group are from the inferior vena cava.

<sup>**</sup> Sample from above renal vein.
**Table 1b.**

Group B (proven adrenal disorders).

Oestrone (Oe₁) and oestradiol (Oe₂) concentrations in inferior vena cava, peripheral and adrenal venous plasma (pg/ml).

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Clinical</th>
<th>Venogram</th>
<th>Oestrogen</th>
<th>Peripheral vein²</th>
<th>Left adrenal vein</th>
<th>Right adrenal vein</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>44</td>
<td>M</td>
<td>Primary aldosteronism</td>
<td>Left adrenal mass</td>
<td>Oe₁</td>
<td>186</td>
<td>222⁴</td>
<td>-</td>
<td>Left adrenal cortical adenoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right normal</td>
<td>Oe₂</td>
<td>202 (A)</td>
<td>62</td>
<td>91</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>M</td>
<td>Primary aldosteronism</td>
<td>Right adrenal mass</td>
<td>Oe₁**</td>
<td>102</td>
<td>-</td>
<td>207⁴</td>
<td>Right adrenal cortical adenoma; gynacomaastia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left normal</td>
<td>Oe₂**</td>
<td>68</td>
<td>-</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>F</td>
<td>Primary aldosteronism</td>
<td>Right adrenal mass</td>
<td>Oe₁</td>
<td>380</td>
<td>289</td>
<td>807⁴</td>
<td>Right adrenal cortical adenoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left normal</td>
<td>Oe₂</td>
<td>117</td>
<td>106</td>
<td>147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>F</td>
<td>Primary aldosteronism</td>
<td>Left adrenal mass</td>
<td>Oe₁</td>
<td>434</td>
<td>259³</td>
<td>326</td>
<td>Left adrenal cortical adenoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right normal</td>
<td>Oe₂</td>
<td>560</td>
<td>276</td>
<td>289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>49</td>
<td>F</td>
<td>Cushing's disease</td>
<td>Left hyperplasia</td>
<td>Oe₁</td>
<td>125</td>
<td>404³</td>
<td>220</td>
<td>Histology:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right normal</td>
<td>Oe₂</td>
<td>84</td>
<td>44</td>
<td>49</td>
<td>Left hyperplasia</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates side of adrenal lesion.
** Antecubital vein sample.
(A) Sample from aorta.
samples were assayed in duplicate at several dose levels between 0.5 and 2 ml of plasma. Adrenal venous, peripheral venous and/or IVC samples from a given patient were assayed simultaneously.

Urinary aldosterone was measured by the double isotope derivative method of Kliman & Peterson (1969). Normal range of urinary aldosterone excretion is 5–17 μg/24 h on a 120 mEq Na diet for 3 days. Plasma renin activity (PRA) was determined by the method of Cohen et al. (1971). Normal values: 120 mEq. Na diet recumbent (2 h) mean 2.5 pg/ml/h with a range of 1.5–3 ng/ml/h; upright (2 h) mean 7.7 with a range of 1.6–17.2 ng/ml/h; 10 mEq. Na diet, recumbent mean 7.1 with a range of 4.9–10.8 ng/ml/h; upright mean 17.2 and range of 6.8–45.8 ng/ml/h.

RESULTS

Group A (see Table 1 a)

All patients, except 2 and 8, had greater concentrations of Oe₂ in adrenal venous plasma than in the IVC or antecubital vein plasma. Patients 2 and 8 had lower concentrations of Oe₂ in the adrenal than in the IVC samples. Antecubital venous samples were not obtained in these patients.

Oe₂ concentrations were greater in the adrenal venous plasma of patients 1, 2, 4, 6 and 7 as compared to IVC or antecubital vein samples. The Oe₂ concentrations in the adrenal venous samples of patients 3 and 5 were comparable to those in the IVC. In patient 8, the adrenal venous Oe₂ concentration was lower than in the IVC.

Patient 5 presented with hypertension and clinical features of Cushing's disease (weight gain, truncal obesity, cervicodorsal hump, rounded facies and hirsutism). The sella turcica was radiologically normal. Baseline 17-hydroxycorticosteroids (17-OHCS) were 8.6 and 9 mg/24 h and 17-ketosteroids (17-KS) 30.1 and 20.2 mg/24 h. Plasma 17-OHCS, determined by a “non-specific” fluorometric procedure, were 27.5 μg/100 ml at 8 a.m. and 16.9 μg/100 ml at 9 p.m. After metyrapone, 750 mg every 4 h for 6 doses, urinary 17-OHCS were 53.3 mg/24 h and 17-KS, 53.2 mg/24 h. Dexamethasone, 2 mg daily for 2 days, decreased 17-OHCS to 2.5 and 17-KS to 15.5 mg/24 h. Dexamethasone (8 mg daily) for 2 additional days further decreased 17-OHCS to 1.1 and 17-KS to 6.0 mg/24 h. The diminished circadian rhythm of the plasma 17-OHCS and the response of urinary 17-OHCS to metyrapone were interpreted as signs of mild Cushing's disease, secondary to non-neoplastic adrenal cortical hyperfunction. The adrenal venogram was normal. A definitive diagnosis was precluded by adrenal infarction at the time of venography. No other complications occurred in this series.

Patient 6 had hirsutism and oligomenorrhea and a 17-KS excretion of 13.8 mg/24 h which did not increase on 4 mg of dexamethasone daily for 7 days. 17-OHCS excretion was normal.
Plasma renin activity and urinary aldosterone excretion in patients 3, 7 and 8 in whom an adrenal cortical adenoma was not demonstrable. Patient 10 had primary aldosteronism (Conn's syndrome).

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Plasma renin activity ng/ml/h</th>
<th>Urinary aldosterone excretion µg/24 h</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>120 mEq. Na Reclining</td>
<td>10 mEq. Na Reclining</td>
<td>120 mEq. Na Upright</td>
</tr>
<tr>
<td>3</td>
<td>1.85*</td>
<td>1.5*</td>
<td>19.2</td>
</tr>
<tr>
<td>7</td>
<td>0.14</td>
<td>0.04</td>
<td>0.25</td>
</tr>
<tr>
<td>8</td>
<td>0.74</td>
<td>1.9</td>
<td>10.7</td>
</tr>
<tr>
<td>10</td>
<td>Below</td>
<td>1</td>
<td>183</td>
</tr>
</tbody>
</table>

PREOP = Prior to removal of a 3 cm right adrenal cortical adenoma.
POSTOP = 6 months following removal of the adenoma.
* = Patient ambulant for 24 h.
** = On 10 mEq. Na diet for 3 days.

Values for aldosterone excretion and PRA in patients 3, 7, 8 and 10 are summarized in Table 2. Patients 1 and 2 had essential hypertension with normal aldosterone excretion and PRA. Patient 3 had hypertension with elevated urinary aldosterone and suppression of PRA. Although no abnormality could be demonstrated radiologically, this patient may have a small aldosterone secreting adenoma. Patient 4 was hypertensive with a normal adrenal venogram (aldosterone and PRA values are not available). Patients 7 and 8 had low renin hypertension (normal aldosterone excretion and suppression of PRA).

Group B (see Table 1b)

Patients 9–11 had Oe1 and Oe2 concentrations in adrenal venous plasma greater than in peripheral plasma. Patient 10 was a 32 year old male with
bilateral breast enlargement at the time of adrenal catheterization. Spironolactone therapy, 100–150 mg daily, had been instituted 4 months previously. Following resection of a 3 cm right adrenocortical adenoma, all abnormalities (see Table 2 for laboratory values) returned to normal. Patient 12 had lower Oe₁ and Oe₂ concentrations in both adrenal veins than in the IVC. Patient 13 had a concentration of Oe₁ in the left adrenal venous plasma considerably higher (404 pg/ml) than in the contralateral adrenal venous sample (220 pg/ml) or the IVC (125 pg/ml). Oe₂ values in the adrenal venous samples were lower than in the IVC.

DISCUSSION

Direct proof of the secretion of a hormone requires the demonstration of a greater concentration in the venous effluent of the gland than in arterial or peripheral blood.

The present study demonstrates the secretion of Oe₁ and Oe₂ by the adrenal gland in the majority of patients studied. This was true for patients with and without demonstrable neoplastic disease. Patients 1 and 2 were free of adrenal abnormalities. Oe₁ and Oe₂ gradients were present in the adrenal venous plasma of the former patient, while in the latter there was an Oe₂ gradient.

Grant et al. (1957) reported values for adrenal blood flow of 0.39 to 1.9 ml/min for a single gland. After ACTH administration, this value increased to between 1 and 6 ml/min. Doubling the latter value yields a maximum blood flow of 12 ml/min or approximately 7 ml/min maximum adrenal plasma flow. To estimate adrenal secretion rates, the following expression was utilized: adrenal secretion rate = adrenal plasma flow \( \times \Delta \), (where \( \Delta \) = differential in Oe₁ and Oe₂ concentration between the adrenal venous and peripheral plasma). Patients 1, 9 and 10 were chosen for this calculation as samples from the IVC in the remaining patients were obtained without reference to the level of entry of the renal or gonadal veins. It is thus possible that some oestrogen concentrations in the IVC may not reflect solely peripheral concentrations if the samples were obtained close to the gonadal or renal veins. In patient 9, in whom blood from the aorta and left adrenal vein was utilized for assay, the adrenal secretion rate for Oe₁ was 0.2 \( \mu g/\text{day} \) and that for Oe₂ 0.5 \( \mu g/\text{day} \). In patient 1, these values were 2 \( \mu g/\text{day} \) (Oe₁) and 0.2 \( \mu g/\text{day} \) (Oe₂), while in patient 10 they were 1 \( \mu g/\text{day} \) and 0.1 \( \mu g/\text{day} \), respectively. These estimates are in agreement with those of Baird et al. (1969) who suggested that adrenal secretion rates of Oe₁ probably do not exceed 10 \( \mu g/\text{day} \) in either sex.

In 1968, Baird reported that the blood production rate of Oe₂ was 39 \( \mu g/\text{day} \) in normal men. Estimates of Oe₁ blood production rates range from 54 \( \mu g/\text{day} \) (Longcope 1972) to 158 \( \mu g/\text{day} \) (Baird 1968). This variability in Oe₁ blood production estimates may result from differences in methods for measuring.
Oe1 concentrations, the time of day the studies are performed and the posture of the subject during the experiment. A comparison of our estimates of adrenal secretion with the minimum reported values for the Oe1 blood production rate, indicates that adrenal secretion accounts for less than 4 % of Oe1 and less than 2 % of Oe2 production.

Patient 10 was the only individual in whom clinical evidence of an oestrogen effect was present. The modestly increased concentration of Oe1 (102 pg/ml) and Oe2 (68 pg/ml) in peripheral plasma suggest an overproduction of both oestrogens. However, the low adrenal secretion rates suggest that the source of the excess oestrogens was not the adrenal gland. These observations are compatible with the high Oe1 and Oe2 production rates reported by Kirschner & Taylor (1972) in males with gynaecomastia from diverse causes. In their study (and perhaps in patient 10) the excess of Oe1 production was accounted for by a higher peripheral conversion of androstenedione.

The highest value for Oe1 was 893 pg/ml in the adrenal venous plasma of patient 4 (IVC concentration of 136 pg/ml). The explanation for this is not apparent as the patient had been on dexamethasone for 3 days at the time of sampling. This individual, as well as patient 7, had a higher concentration of Oe2 in the adrenal venous plasma than in the IVC despite dexamethasone therapy. Patient 12 had Oe1 and Oe2 concentrations in both adrenal samples considerably lower than in the IVC. This may have been a result of the IVC sample being obtained high, near the renal or gonadal veins. Alternatively, the high Oe2 concentration may be compatible with the pre-ovulatory oestrogen peak.

Considering the reported values for adrenal venous dehydroepiandrosterone (Saez et al. 1972), the cross-reactivity studies and the chromatographic purification used in our assay, it is unlikely that the Oe1 and Oe2 concentrations in the adrenal venous plasma were significantly affected by other adrenal steroids.

The limited data presented herein, taken together with other studies (Baird 1968; Longcope 1972), suggest that at least 96 % of the total Oe1 and 98 % of the total Oe2 blood production rates of male subjects are derived from sources other than adrenal secretion. This would include Oe1 from peripheral conversion of precursors (MacDonald et al. 1967) and secretion of Oe1 and Oe2 by the testis (Kelch et al. 1972; Longcope et al. 1972). Our results suggest that both Oe1 and Oe2 are secreted by the adrenal in neoplastic and non-neoplastic disorders in detectable but small amounts.

ACKNOWLEDGMENTS

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