Oestrogen metabolism and excretion in liver disease

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EDITORIAL SYNOPSIS  Raised urinary oestrogen excretion was noted in 16 men and women with liver disease. The study suggests that the increased output of urinary oestrogens was usually due to increased secretion rates of the primary oestrogenic hormones rather than to impaired oestrogen metabolism by the liver.

Numerous workers have reported a raised output of urinary oestrogens in men and women with various types of liver disease. Glass, Edmonson, and Soll (1940), Rupp, Cantarow, Rakoff, and Paschkis (1951), Pincus, Rakoff, Cohen, and Tumen (1951), and Dohan, Richardson, Blumle, and György (1952), using bioassay methods, all found in approximately 48% of the patients studied values which usually were less than twice the normal maximum but occasionally were as high as seven times the normal. Later workers, using colorimetric measurements, have investigated a smaller number of patients and have found raised values in only approximately 20% of the cases, and no value has exceeded twice the normal maximum (Cameron, 1957; Lyngbye and Mogensen, 1961). This raised output has been attributed to impaired metabolism by the diseased liver but evidence for this concept has been conflicting. Glass, Edmonson, and Soll (1944) administered oestrone and oestradiol to three patients with liver disease and recovered 83-86% of the biological activity of the administered dose in the urine whereas values of 10% would have been expected for normal individuals. On the other hand, Dohan et al. (1952) and Cameron (1957) measured endogenous urinary oestriol, oestrone, and oestradiol separately and found that the major urinary oestrogen in liver disease is often oestriol, which is the least biologically active of the three. After the administration of oestrone, oestradiol, or their esters to patients with liver disease, Stea, Bassoé, and Emberland (1958), in a study of five cases, found a decreased recovery as the three oestrogens in two and an increased recovery in one, and Lyngbye and Mogensen (1961) in five cases found normal overall recoveries but in two the recovery as oestradiol was increased at the expense of the oestriol. The metabolic pattern described by the different workers has therefore not been consistent.

During the past five years we have had the opportunity of studying oestrogen output and metabolism in a group of patients with various types of liver disease. Although the results in general conform with those already reported, two patients with particularly high oestrogen outputs were encountered, and these are presented with our general findings, since similar values have not previously been reported using chemical assay methods.

THE INVESTIGATION

OESTROGEN MEASUREMENT The urinary excretion of oestriol, oestrone, and oestradiol was measured by the method of Brown (1955) as modified by Brown, Bulbrook, and Greenwood (1957). The urine specimens from London were collected in polythene bottles, deep frozen, packed in straw, and despatched to Edinburgh for assay.

The endogenous oestrogen output was measured on at least two 24- or 48-hour urine collections. Metabolic experiments were performed by administering oestradiol, 2.5 mg. intramuscularly in olive oil, and determining the increased output of urinary oestriol, oestrone, and oestradiol during the next six consecutive days. The results of these measurements are summarized in the Table. No correction was made for losses of oestrogens occurring in the assay procedure.

PATIENTS Studies were made on 13 men and three women with liver disease. Their age, sex, and type and severity of liver disease are listed in the Table. Stigmata of chronic liver disease (clubbing of the fingers, spider naevi, and palmar erythema) were noted in cases 1, 8, 10, 11, and 12. Endocrine changes were also observed as follows: gynaecomastia (cases 1 and 4), testicular atrophy

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Table

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical Particulars</th>
<th>Biliuria</th>
<th>Endogenous Oestrogens (µg/24 hr. urine)</th>
<th>Exogenous Oestrogens (% of dose recovered)</th>
<th>Oestriol</th>
<th>Oestrone</th>
<th>Oestradiol</th>
<th>Total</th>
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<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>M</td>
<td>Terminal Day 1</td>
<td>+</td>
<td>326  55  15  396</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>M</td>
<td>Severe, Nov. 1960</td>
<td>+</td>
<td>2 6  3  2  0  5  8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>F</td>
<td>Terminal studied after portocaval shunt</td>
<td>+</td>
<td>6.5  15  0  9  23.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>Mild</td>
<td>+</td>
<td>14.5  2.2  1  16.5*</td>
<td>19.0  1.9  0.8  21.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>Mild</td>
<td>-</td>
<td>18.5  1.9  1  20.4*</td>
<td>11.1  1.0  1.4  13.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>M</td>
<td>Mild</td>
<td>-</td>
<td>18.6  3.0  1.3  22.9</td>
<td>6.7  2.8  1.5  11.0</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>35</td>
<td>M</td>
<td>Severe, Oct. 1958</td>
<td>+</td>
<td>19.7  10.0  1.8  32.3</td>
<td>9.8  7.2  3.7  20.7</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>47</td>
<td>M</td>
<td>Severe</td>
<td>+</td>
<td>14.7  6.1  0.4  21.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>39</td>
<td>F</td>
<td>Severe</td>
<td>+</td>
<td>10.0  8.8  0.9  19.7</td>
<td>4.3  5.6  2.3  12.2</td>
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<td></td>
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<tr>
<td>10</td>
<td>44</td>
<td>M</td>
<td>Severe</td>
<td>+</td>
<td>18.5  3.6  0.3  22.4</td>
<td>9.4  1.5  1.2  12.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>M</td>
<td>Moderate, hepatoma</td>
<td>-</td>
<td>6.6  8.7  2.5  17.8</td>
<td>3.6  4.0  2.2  9.8</td>
<td></td>
<td></td>
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<tr>
<td>12</td>
<td>67</td>
<td>M</td>
<td>Moderate</td>
<td>+</td>
<td>11.2  4.1  0.7  16.0</td>
<td>2.5  1.1  0.6  4.2</td>
<td></td>
<td></td>
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<tr>
<td>13</td>
<td>53</td>
<td>M</td>
<td>Mild</td>
<td>-</td>
<td>9.5  3.4  0.3  13.2</td>
<td>15.6  4.3  2.9  22.8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>14</td>
<td>50</td>
<td>M</td>
<td>Carcinomatosis of liver</td>
<td>+</td>
<td>33.7  3.2  1.7  38.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>15</td>
<td>60</td>
<td>F</td>
<td>Carcinoma of pancreas</td>
<td>+</td>
<td>3.4  2.1  1  5.5*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>64</td>
<td>M</td>
<td>Stone with biliary cirrhosis</td>
<td>+</td>
<td>10.2  3.1  1  13.3*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal Values

<table>
<thead>
<tr>
<th>Men (24) (Ginsburg and Brown, 1961)</th>
<th>Range</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-9 ± 1-1</td>
<td>4-7 ± 2-7</td>
</tr>
<tr>
<td></td>
<td>2-8 ± 2-9</td>
<td>3-0 ± 1-3</td>
</tr>
<tr>
<td></td>
<td>0-2 ± 0-8</td>
<td>1-3 ± 0-7</td>
</tr>
<tr>
<td></td>
<td>7-2 ± 1-9</td>
<td>11-1 ± 3-1</td>
</tr>
</tbody>
</table>

Post-menopausal women (10) (Brown, Kellar, and Matthew (1959))

<table>
<thead>
<tr>
<th>Range</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-7 ± 2-5</td>
<td>3-5 ± 1-3</td>
</tr>
<tr>
<td>0-3 ± 0-4</td>
<td>1-1 ± 0-3</td>
</tr>
<tr>
<td>3-2 ± 0-9</td>
<td>4-3 ± 1-1</td>
</tr>
</tbody>
</table>

Mild = no clinical manifestations of liver disease, diagnosis made by liver biopsy.
Moderate = clinical evidence for liver disease but without severe complications.
Severe = severe complications of liver disease, including portal hypertension, ascites, and neuro-psychiatric manifestations.
Terminal = dying within one week with severe complications but not comatose at the time of study.

1) Implies interference in the oestradiol measurements.
2) No. of cases.

(cases 4, 5, and 7), and amenorrhoea (case 9). Biochemical tests of liver function were performed in many instances and the results in general confirmed the diagnosis made on clinical and histological evidence. Further details of the two patients with particularly abnormal values for urinary oestrogens were as follows.

**Case 1** This man was a chronic alcoholic. Evidence of cirrhosis of the liver was noted in 1953 at the age of 36 years. Right gynaecomastia was observed in 1956, and in 1957 he was admitted in impending hepatic failure with jaundice, haematemesis, oedema, ascites, neuro-psychiatric manifestations, clubbing of the fingers, and spider naevi. He was treated by splenectomy on 19 September 1957, and later required a laparotomy for obstruction and peritonitis on 24 September. Urines were collected for assay on 28 and 29 September. He lapsed into hepatic coma and died on 2 October.

**Case 7** This man contracted infectious hepatitis in 1944 at the age of 22 years. This was followed by slowly progressive cirrhosis with fluctuating jaundice and oedema. In October 1957, when the first study was made, the patient was suffering from jaundice (serum bilirubin 2.4 mg.%), oedema, and neuro-psychiatric manifestations. He deteriorated rapidly and in February 1958, when the second study was made, he was deeply jaundiced (serum bilirubin 27.5 mg.%). He lapsed into coma two days after the study and died two days after this. At necropsy, the liver showed gross post-necrotic cirrhosis, the testes showed diminished spermatogenesis but the pituitary, adrenals, thyroid, and prostate appeared normal.

**RESULTS**

The results of the investigation are summarized in the Table. In some patients there was interference in the oestradiol measurements as indicated by negative values following spectrophotometric
correction, and in these cases the true ‘total’ figures were probably slightly higher than those given.

Grossly abnormal oestrogen figures were found in the two patients, cases 1 and 7. Case 1 was excreting
twenty times the normal maximum on the second
day; in both instances the output of all three
oestrogens was elevated and oestriol was the major
oestrogen. Case 7, in October 1957, had a moderately
increased total output, and oestriol was the major
oestrogen; the recovery of administered oestradiol
was normal, the ratios of the three oestrogens
recovered resembling those of the endogenous
output. In February 1958, the total excretion had
increased to more than three times the normal
maximum, and, of this, the major portion was
oestrone with practically no oestriol. Of the remain-
ing 14 patients, seven (cases 3, 5, 6, 8, 9, 10, 14) were
excreting ‘total’ amounts of oestrogens which were
one to two times the maximum figures found in
normal men and post-menopausal women. In six of
these the increase was mainly in the output of
oestriol, and in one only (case 3) was it confined to
the oestrone.

Metabolic experiments were performed in nine
patients (cases 4, 5, 6, 7, 9, 10, 11, 12, 13). In
eight of these, who included four of the patients with
a higher endogenous output than normal, the total
recovery was within the normal range, the mean
(15·5%) comparing with the mean figures of 16·0%
and 14·7% reported by Brown (1957, 1958). The
ratios of the three oestrogens recovered resembled
does of the endogenous output, and in four
patients (cases 4, 5, 10, 13) the proportion of
oestradiol relative to oestrone and oestradiol was
greater than normal; in three of the cases (nos. 5, 10,
13) the recovery as oestradiol approached or
exceeded the amount in the oestriol fraction,
whereas in normals urinary oestriol is generally
less than half the oestrone. An abnormal ‘total’
recovery was found in only one patient (case 12), the
figure being less than half the normal minimum, and
in this case again oestriol was the major metabolite.

**DISCUSSION**

The results obtained here demonstrate most of the
abnormalities in oestrogen output and metabolism
which have been reported in liver disease. Thus, the
occasional very high values previously obtained
only by bioassay methods have now been demon-
strated by a chemical assay procedure. The propor-
tion of patients (56%) with an elevated excretion
of urinary oestrogens is higher than in any other
group previously reported, a finding which is
probably the result of selecting individuals who were
most likely to show abnormalities, such as those four
with severe complications and the three in terminal
liver failure. As shown by Dohan et al. (1952) and
Cameron (1957) the proportion of oestriol to the
other endogenous oestrogens excreted was higher
than normal in many patients, indicating that meta-
bolism to this oestrogen is often enhanced in liver
disease. However, in two instances (cases 3, 7) the
increase was confined to the oestriol fraction, as in
the case reported by Lyngbye and Mogensen (1961).
In the metabolism experiments, the overall recovery
of administered oestradiol as urinary oestriol,
oestrone, and oestradiol, was usually normal but
occasionally low, as reported by Støa et al. (1958) and
Lyngbye and Mogensen (1961): no high recoveries
similar to those reported by Glass et al. (1944) were
obtained. The ratio of oestradiol to other oestrogens
recovered was usually higher than normal, indicating
an increased conversion, but such a finding is not
confined to liver disease and has been reported in
other diseases, such as breast cancer and coronary
disease (Brown, 1958; Bauld, Givner, and Milne,
1957). Occasionally the ratio of oestradiol to
oestrone was increased, as was demonstrated by
Lyngbye and Mogensen (1961).

The two patients with particularly abnormal
oestrogen levels merit special discussion. During his
first investigation, case 7 was excreting oestriol,
oestrone, and oestradiol in amounts which were
greater than normal but within the range found in
the majority of patients with liver disease. At this
time, the overall recovery of administered oestradiol
was normal and oestradiol was the major metabolite.
The picture had changed markedly four months
later, when the patient was in terminal liver failure:
the overall oestrogen output had increased, oestrone
was the major urinary oestrogen, and the output of
oestradiol had virtually ceased. This indicated that the
capacity of the liver to convert oestrone to oestradiol
had almost been abolished at this extreme stage of
the disease. If the determination had been made by
bioassay, the high oestrone output would have
registered as a markedly increased output of
oestrogenic activity. This was the only case in the
series which provided evidence that metabolism of
oestradiol and oestrone to oestriol may be impaired
in liver disease. Case 1, with the highest oestro-
gen output encountered, was also in terminal liver
failure when he was studied. However, in this case,
all three of the oestrogen fractions were markedly
elevated with oestriol predominating as the major
metabolite. There was therefore no evidence in this
case of impaired oestrogen metabolism by the liver.
This patient’s history was complicated by the fact
that splenectomy and then an exploratory lapar-
otomy had been performed several days before the
study, and the high but falling oestrogen levels
might have been caused by the adrenal responses to
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the two operations. However, these were exceptionally high levels, and beyond the response obtained by maximum stimulation of the adrenals with corticotrophin (Brown, Falconer, and Strong, 1959). No correlation could be demonstrated between abnormalities in oestrogen output and the severity of the liver disease as judged by clinical, histological, or biochemical findings. Although the abnormalities tended to be more common and more marked among those patients who were in the terminal stages of the disease, they also occurred in some of the mild cases of cirrhosis. The suggestion has frequently been made that various stigmata of liver disease, such as spider naevi and palmar erythema, and some of the endocrine changes such as gynaecomastia, are caused by raised oestrogen levels (Bean, 1959). In the present series, no such direct connexion could be demonstrated, a finding which is in agreement with that of Cameron (1957).

The metabolism experiments show that the raised urinary outputs of endogenous oestrogens found in liver disease are due in most instances to raised secretion rates of the primary oestrogenic hormone. The finding that the ratio of oestradiol to oestrone and oestradiol in the urine is usually greater than normal shows that the diseased liver may actually have an increased capacity for metabolizing oestradiol and oestrone to oestriol. These experiments, however, provide no information concerning impairment or otherwise of the other metabolic pathways. Further investigation is obviously required to determine the source of the increased output of oestrogens. Raised urinary oestrogen levels have also been reported in hypertrrophic pulmonary osteoarthropathy associated with bronchial carcinoma (Ginsburg and Brown, 1961) where there was no evidence of liver disease and no demonstrable abnormality of oestrogen metabolism. It is possible that the sources of the abnormal amounts of oestrogens are the same in the two disorders.

SUMMARY

Raised urinary oestrogen excretion was found in nine of 16 men and women with liver disease. The increased values were generally less than twice the normal maximum but one patient was excreting twenty times the normal maximum. The major urinary oestrogen was usually oestrone but occasionally it was oestradiol. These results indicate that, with one possible exception, the increased output of urinary oestrogens was due to increased secretion rates of the primary oestrogenic hormone rather than to impaired oestrogen metabolism by the liver.

Abnormalities in oestrogen output were most marked and common in terminal liver failure but they also occurred in mild cirrhosis.

These findings are in agreement with many already published using either bioassay or chemical techniques.

We wish to thank Dr. W. I. Card, Dr. W. Sircus, and Dr. R. W. D. Turner for access to their patients, and Mrs. Janet Blair and Miss Wilma McGillivray for technical assistance with the analyses. The endowment fund of St. Thomas's Hospital defrayed some of the expenses in sending specimens from London.

REFERENCES


