To the Editor: It has recently been suggested that the oral cholecys
tographic contrast agents iopanoic acid and sodium ipodate may be
useful in the management of hyperthyroidism. 1,2 However, as noted in
the recent discussion by Larsen, the duration of their effects on
iodothyronine monodeiodination and the long-term results of this
form of treatment are still unclear. Thyroid-uptake studies indicate
that these compounds deliver a substantial iodine load, raising the
possibility of later exacerbation of hyperthyroidism when autono-
mous tissue is present.

We have recently evaluated the effects of these agents in two
patients with mild hyperthyroidism who presented for gynecologic
surgery. The first was a 41-year-old woman, treated 10 years before
with radioactive iodine for hyperthyroidism, who was admitted for
an abdominal hysterectomy. The thyroid was smoothly enlarged,
and mild bilateral protrusion indicated probable Graves' disease. The
second patient was a 71-year-old woman admitted for a vaginal
repair. Hyperthyroidism, associated with a small multinodular goi-
ter, had been diagnosed two years previously and treated with pro-
phyliothiamin for one year. Because both patients had only equivocal
clinical features of hyperthyroidism, we elected not to delay surgery.
Blood was taken, and 3 g of ipanoic acid was given orally 18 to 24
hours before the operation. Postoperative recovery was uncompli-
cated, associated with the expected decrease in serum T4 (Table 1).
However, when reviewed

| Table 1. Thyroid Function after Iopanoic Acid
| Administration. |
|-----------------|-----------------|-----------------|
| PATIENT NO. | DAYS BEFORE | THYROIDINE | FREE-THYROIDINE | THROIDO-
| OR AFTER | wg/dl | wg/dl | INDEX | THYRONINE |
| SURGERY | | | | | |
| 1 | -1 | 15.0 | 14.4 | 220 |
| | 1 | 10.1 | 10.4 | 65 |
| | +3 | 10.5 | 10.7 | 34 |
| | 5 | 12.6 | 12.5 | 52 |
| | +34 | 19.1 | 22.2 | 310 |
| 2 | -1 | 10.4 | 10.5 | 195 |
| | +1 | 9.3 | 9.9 | 72 |
| | +6 | 9.9 | 9.5 | 65 |
| | 9 | 9.5 | 8.9 | 79 |
| | +26 | 14.6 | 16.5 | 280 |
| Normal range | 4.5-11 | 4.0-11 | 75-175 |

four to five weeks after surgery, both patients appeared to be clearly
hyperthyroid, with heat intolerance, tachycardia, and tremor. Bio-
chemical assessment (Table 1) confirmed that hyperthyroidism was
more severe than it had been before surgery. A similar sequence is
well recognized after cholecystography in European endemic-goiter
areas.3 Although such findings do not rule out the use of oral chole-
cystographic contrast agents in the management of hyperthyroid-
ism, their use without conventional antithyroid drugs would seem
unwise. If used alone, a gratifying early biochemical response may
be followed by exacerbation of hyperthyroidism several weeks later.

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J. R. STOCKIGT, M.D.

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1. Wu S-Y, Chopa IJ, Solomon DH, Bennett LR. Changes in circulating
iodothyronines in euthyroid and hyperthyroid subjects given ipodate (Orgafrin,
2. Sharp B, Reed AW, Tanagana EI, Geffen DL, Hershman JM. Treatment of
hyperthyroidism with sodium ipodate (Orgafrin) in addition to propylthiour~。
3. Herrmann J, Kriskemper HL. Gâ€”fähigung von Patienten mit latenten
und manifesten Hyperthyreose durch jodhaltige Röntgenkontrastmittel und Medii-

The above letters were referred to the author of the article in
question, who offers the following reply:

To the Editor: Drs. Kleinmann and Braverman raise a question
about my interpretation of their study of the effects of iopanoic acid
on the human pituitary-thyroid axis. We differ because in my opin-
ion the authors have not compared their experimental data with the
most suitable control. As they state in their letter, in subjects receiv-
ing iopanoic acid plus T4, the TRH-induced TSH response was not
different from that found in the same persons before any medication
was given. Since the dose of T4 used (25 µg per day for two days)
causes a substantial suppression of TRH-induced TSH release and in
fact reduced the response by 50 per cent in these same four
subjects, this is the more appropriate control for comparison. If T4
given with iopanoic acid prevented the effect of the iopanoic acid
on the TSH response to TRH, then the response to iopanoic acid plus
T4 should have been identical to that found when T4 was given
alone. The peak TSH increment after iopanoic acid plus T4 was 20
µU per milliliter, as compared with 9 µU per milliliter after T4 alone,
and therefore was not normalized. Although a final conclu-
sion is not justified on the basis of results in only four subjects, their
findings suggest that iopanoic acid can decrease thyroid hormone
feedback suppression of TSH release in human beings by a mecha-
nism that is independent of (though additive to) the effect of the con-
comitant decrease in serum T4. The most likely explanation for
this, on the basis of animal studies, is that iopanoic acid inhibits
intrapituitary conversion of T4 to T3.1-3

I certainly agree with Drs. Kleinmann and Braverman that the
circulating T3 concentration is an important regulator of TSH
secretion. The major emphasis of my discussion, however, was that
serum T4, through its intrapituitary conversion to T3, is likely to be
equally important. Agents that interfere with pituitary conversion of
T4 to T3, such as iopanoic acid, can be expected to increase TSH
secretion independently of the fall in serum T4.

Fuller and Stockigt provide two examples of a problem that may
occur when iodine-containing agents of any type are administered
to patients with hyperthyroidism. I subscribe to their recommendation
that a thionamide be given in combination if oral cholecystographic
agents are to be used in such patients to block conversion of T4
to T3. In addition, since there is a potential for prolonged increases
in total-body iodine stores because of the slow excretion of these
compounds, one should also avoid such agents if 131I therapy
is planned for the near future.

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1. Larsen PR, Dick TE, Markovitz BP, Kaplan MM, Gard TG. Inhibition of
intrapituitary thyroxine to 3,5,3'-triiodothyronine conversion prevents the
acute suppression of thyrotropin release by thyroxine in hypothyroid rats.
F. Evidence against a major role of L-thyroxine at the pituitary level: studies in
rats treated with iopanoic acid (Telepaque). Endocrinology. 1980; 105:1827-
3. Cheron RG, Kaplan MM, Larsen PR. Physiological and pharmacological
influences on thyroxine to 3,5,3',triiodothyronine conversion and nuclear
3,5,3'-triiodothyronine binding in rat anterior pituitary. J Clin Invest. 1979;
64:1402-14.

EFFECT OF THE HEMODIALYSIS PRESCRIPTION ON MORBIDITY

To the Editor: A key question raised by the article of Lowrie et al.1
in the November 12 issue deserves discussion: Does blood urea
nitrogen (BUN) reflect the adequacy of dialysis in all instances? In
other words, does BUN extraction parallel that of middle molecules,
including uricemic toxins?2 We would like to report the results of a
study conducted in our center during the past five years.

Two groups of patients on hemodialysis without dietary protein
restriction were compared, as indicated in Table 1. Group I under-
drew dialysis with the highly permeable membrane AN69 (RP 6,
1 m²) and the Rhodial system (Hospal) for careful ultrafiltration
monitoring, and Group II underwent dialysis with a cuprophan
membrane (1 m²) and an open-circuit system in order to obtain a
dialytic index > 1, as proposed by Babb et al.,3 so that the length of
the dialysis treatment was defined a priori for each patient. Since the

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Table 1. Characteristics and Main Results Obtained in Dialysis with a 1-m² Highly Permeable Membrane (AN69) and with a 1-m² Cuprophane Membrane.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>GROUP I</th>
<th>GROUP II</th>
<th>P VALUE *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis membrane</td>
<td>Polycrylonitrile (AN69)</td>
<td>Cuprophane</td>
<td>—</td>
</tr>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>70</td>
<td>—</td>
</tr>
<tr>
<td>Age (yr) †</td>
<td>44.3±2.8</td>
<td>44.9±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Residual creatinine clearance (mL/min) †</td>
<td>0.5±0.1</td>
<td>0.4±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Blood-flow rate (mL/min) †</td>
<td>231±6</td>
<td>224±7</td>
<td>NS</td>
</tr>
<tr>
<td>Total no. of dialysis sessions</td>
<td>19,342</td>
<td>19,212</td>
<td></td>
</tr>
<tr>
<td><strong>Results of dialysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (hr/wk) †</td>
<td>9.5±0.2</td>
<td>16.4±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-dialysis BUN (mg/dL) †</td>
<td>88±1.1</td>
<td>72±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-dialysis BUN (mg/dL) †</td>
<td>46.0±0.1</td>
<td>29.0±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Tolerance of dialysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of minor disturbances (per 100 sessions) † †</td>
<td>9.7±1.2</td>
<td>15.8±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization rate (days/patient/yr) †</td>
<td>4.9±0.8</td>
<td>7.3±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of deaths in 5 yr</td>
<td>15</td>
<td>12</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P values were obtained with Student’s t-test. NS denotes not significant.
†Mean ± S.E.M.
‡Minor disturbances include nausea, vomiting, transient hypotension, and cramps.

Rhodial system is a closed circuit with a tank of 75 liters of dialysis bath, recirculation led to a higher BUN level in patients treated with AN69 membranes than in patients treated with cuprophane membranes. In spite of a lower BUN removal, patients with AN69 membranes spent less time on dialysis than patients with cuprophane membranes and were hospitalized less frequently.

We conclude that BUN extraction may be a valuable index of the adequacy of dialysis in a comparison of different dialytic strategies using the same type of artificial membrane. When highly permeable membranes are taken into account, it is obvious that molecules in the range of "middle molecules" are extracted to a higher extent than with less permeable membranes, and that some middle molecules are toxic to the uremic patient.

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The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: One cannot assume that dietary protein intake is the same in two groups of patients on an unrestricted diet, and the patients of Brunonis et al. treated with AN69 membranes may have eaten substantially more or substantially less than the others. Furthermore, the dietary intake of nutrients is probably responsive to the dialysis prescriptions.* The higher BUN in the AN69 group could have resulted from shorter dialysis time as well as dialysate recirculation. Similarly, the different rates of "minor disturbances" could have resulted from better control of ultrafiltration or from a lesser opportunity for symptoms because of a shorter treatment time. The ratio of times (9.5 to 16.4 hours per week) is about the same as the ratio of disturbance rates (9.7 to 15.8 per 100 sessions), for example, and the different disturbance rates could thus be explained without resorting to unidentified "middle molecules." The 2.4-day difference in hospitalization is subject to great bias (the S.E.M. in Group II is nearly twice that in Group I) and cannot be evaluated analytically from the data presented. Finally, their Group I was probably not terribly different from our Group III, and their Group II was not much different from our Group I — both had low BUN.

It is true that the National Cooperative Dialysis Study used only cellulosic membranes to perform dialysis. Nonetheless, we respectfully disagree with the "obvious" conclusion of Brunonis et al. and submit that there is little well-controlled evidence suggesting that the hypothetical middle molecule has much to do with symptomatic uremia. We only wish that some investigator had clearly and reproducibly identified a few of them during the past 10 years. Nonetheless, urea, when evaluated in the light of protein intake, appears to be a reasonable surrogate molecule by which dialysis may be prescribed, regardless of the existence of middle or other molecules.

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DEPRESSIVE DISORDERS AND HLA

To the Editor: In the article by Weitkamp et al. on "Depressive Disorders and HLA" (November 26 issue)† siblings of affected probands were considered unaffected (i.e., without an affective disorder) if they did not manifest a depressive illness by the age of 30. Although the authors explain that they do not expect all such siblings to remain unaffected, this arbitrary age criterion limits the conclusions that can be drawn from the study. Although a positive family history is associated with a younger age at the onset of affective disorders, probably less than half the patients in whom an affective disorder develops have one by age 30. If the subjects under study could be followed for a decade or longer to see whether an affective disorder emerged, reanalysis of the data would be of great interest. If the initial findings were confirmed, they would constitute very impressive evidence that vulnerability to depression was related to chromosome 6. Alternatively, reanalysis might suggest evidence of separate affective disorders with differing genetic backgrounds.‡

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The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: The decision to score unaffected offspring over age 30 as having a lower genetic susceptibility to depressive disorder than their affected siblings was made for purposes of analysis. The comparison of interest is, of course, the distribution of HLA haplotypes in relation to the presumed distribution of susceptibility genes. There is precedent for using an age limit as low as 25 years for classifying a person as probably unaffected.* More important, we
