To the Editor: It has recently been suggested that the oral cholecystographic 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 autonomous 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 proptosis indicated probable Graves' disease. The second patient was a 71-year-old woman admitted for a vaginal repair. Hyperthyroidism, associated with a small multinodular goiter, had been diagnosed two years previously and treated with propylthiouracil 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 iopanoic acid was given orally 18 to 24 hours before the operation.

Postoperative recovery was uncomplicated, associated with the expected decrease in serum T_3 (Table 1). However, when reviewed

Table 1. Thyroid Function after Iopanoic Acid Administration.

Patient No.	Days before or after Surgery	Thyroxine	Free-Thyroxine Index	Triiodothyronine
		μg/dl	ng/dl	ng/dl
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. Biochemical 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 cholecystographic contrast agents in the management of hyperthyroidism, 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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1. Wu S-Y, Chopra I J, Solomon DH, Bennett LR. Changes in circulating iodothyronines in euthyroid and hyperthyroid subjects given ipodate (Oragrafin), an agent for oral cholecystography. J Clin Endocrinol Metab. 1978; 46:691-7.
2. Sharp B, Reed AW, Tamagna EI, Geffner DL, Hershman JM. Treatment of hyperthyroidism with sodium ipodate (Oragrafin) in addition to propylthiouracil and propranolol. J Clin Endocrinol Metab. 1981; 53:622-5.
3. Herrmann J, Krüskemper HL. Gefährdung von Patienten mit latenter und manifester Hyperthyreose durch jodhaltige Röntgenkontrastmittel und Medikamente. Dtsch Med Wochenschr. 1978; 103:1434-43.

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 opinion the authors have not compared their experimental data with the most suitable control. As they state in their letter, in subjects receiving iopanoic acid plus T_3, the TRH-induced TSH response was not different from that found in the same persons before any medication was given. Since the dose of T_3 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 T_3 given with iopanoic acid prevented the effect of the iopanoic acid on the TSH response to TRH, then the response to iopanoic acid plus T_3 should have been identical to that found when T_3 was given alone. The peak TSH increment after iopanoic acid plus T_3 was 20 μU per milliliter, as compared with 9 μU per milliliter after T_3 alone, and therefore was not normalized. Although a final conclusion 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 mechanism that is independent of (though additive to) the effect of the concomitant decrease in serum T_3. The most likely explanation for this, on the basis of animal studies, is that iopanoic acid inhibits intrapituitary conversion of T_4 to T_3.[1-3]

I certainly agree with Drs. Kleinmann and Braverman that the circulating T_3 concentration is an important regulator of TSH secretion. The major emphasis of my discussion, however, was that serum T_4, through its intrapituitary conversion to T_3, is likely to be equally important. Agents that interfere with pituitary conversion of T_4 to T_3, such as iopanoic acid, can be expected to increase TSH secretion independently of the fall in serum T_3.

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 T_4 to T_3. 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 ^{131}I 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. J Clin Invest. 1979; 64:117-28.
2. Obregon MJ, Pascual A, Mollol J, Morreale de Escobar G, Escobar del Rey F. Evidence against a major role of L-thyroxine at the pituitary level: studies in rats treated with iopanoic acid (Telepaque). Endocrinology. 1980; 105:1827-35.
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 uremic 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 underwent dialysis with the highly permeable membrane AN69 (RP 6, 1 m^2) and the Rhodial system (Hospal) for careful ultrafiltration monitoring, and Group II underwent dialysis with a cuprophane membrane (1 m^2) 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

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

VARIABLE	GROUP I	GROUP II	P VALUE *
General characteristics			
Dialysis membrane	Polycrylonitrile (AN69)	Cuprophane	—
No. of patients	70	70	—
Age (yr) †	44.3±2.8	44.9±2.7	NS
Residual creatinine clearance (ml/min) †	0.5±0.1	0.4±0.1	NS
Blood-flow rate (ml/min) †	231±6	224±7	NS
Total no. of dialysis sessions	19,342	19,212	—
Results of dialysis			
Duration (hr/wk) †	9.5±0.2	16.4±0.2	<0.001
Pre-dialysis BUN (mg/dl) †	88.8±1.1	72.2±1.0	<0.001
Post-dialysis BUN (mg/dl) †	46.0±0.1	29.0±0.1	<0.001
Tolerance of dialysis			
Rate of minor disturbances (per 100 sessions) †‡	9.7±1.2	15.8±1.7	<0.001
Hospitalization rate (days/patient/yr) †	4.9±0.8	7.3±1.3	<0.001
No. of deaths in 5 yr	15	12	NS

*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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1. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect of the hemodialysis prescription on patient morbidity: report from the National Cooperative Dialysis Study. N Engl J Med. 1981; 305:1176-81.
2. Scribner BH, Babb AL. Retrospective support for the middle molecule hypothesis. In: Proceedings of the VIIth International Congress on Nephrology. Basel: S Karger, 1978:663-7.
3. Babb AL, Strand MJ, Uvelli DA, Milutinovic J, Scribner BH. Quantitative description of dialysis treatment: a dialysis index. Kidney Int [Suppl]. 1975; 2:S23-9.

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 Brunois 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 Brunois 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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*Lowrie EG, Steinberg SM, Galen MA. Factors in the dialysis regimen which contribute to alterations in the abnormalities of uremia. Kidney Int. 1976; 10:409-22.

DEPRESSIVE DISORDERS AND HLA

To the Editor: In the article by Weitkamp et al. on "Depressive Disorders and HLA" (November 26 issue)[1] siblings of an affected proband 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.[2]

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1. Weitkamp LR, Stancer HC, Persad E, Flood C, Guttormsen S. Depressive disorders and HLA: a gene on chromosome 6 that can affect behavior. N Engl J Med. 1981; 305:1301-6.
2. Schlesser MA, Winokur G, Sherman BM. Hypothalamic-pituitary-adrenal axis activity in depressive illness. Arch Gen Psychiatry. 1980; 37:737-43.

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

*Gershon ES, Bunney WE Jr. The question X-linkage in bipolar-manic depressive illness. J Psychiatr Res. 1976; 13:99-117.