pare. The chemical nature of the oligosaccharide bands present in Type III disease is under investigation.

References

John McLaren
Won G. Ng
Thomas Roe

Dept. of Pediatrics
Children's Hosp. of Los Angeles
and the Univ. of Southern California
School of Medicine

1 To whom correspondence should be addressed: Medical Genetics Division, Children’s Hospital of Los Angeles, P.O. Box 54700, Terminal Annex, Los Angeles, CA 90054.

Thyroxine-Binding Globulin Concentrations in the Plasma of Severely Ill Patients

To the Editor:

Plasma thyroid hormone concentrations may be abnormal in non-thyroid disease and pose diagnostic problems. For example, concentrations of triiodothyronine (T3) in the blood decline in acute illness with a reciprocal increase in reverse triiodothyronine (reverse T3), but thyroxine (T4) concentrations are usually normal or only slightly decreased (1, 2). However, McLarty et al. (3) reported that in severely ill patients T4, as well as T3, values may decrease progressively. Because of the parallel changes in the free T4 and T3 indices, they believed that this could not be explained by changes in thyroid hormone-binding proteins. We have noted similar low serum T4 concentrations in severely ill patients but have found significant decreases in the concentration of thyroxine-binding globulin (TBG).

We studied two groups of patients from the Intensive Therapy Unit. The first group (fatalities) consisted of eleven who died as a result of a severe illness of recent onset. There were six with cardiac and (or) respiratory failure, four with severe infection, and one with severe trauma. The second group (survivors) consisted of eleven consecutive patients with similar problems, who responded to therapy: four with cardiac and (or) respiratory failure, two with severe infection, two with trauma, and three severe drug-overdose patients. We compared results from the blood samples obtained on admission for both groups and from the preterminal sample (within 24 h of death) for the fatalities.

Using sera submitted for routine biochemistry, we measured T4 by radioimmunoassay (with polyethylene glycol precipitation). TBG by radioimmunoassay with CIS reagents (TBGK-1), and T3 by Sephadex uptake (T3SU) (4). From these values we calculated both a free thyroxine index (FTI), by the formula T4 × T3SU/100, and the T4/TBG ratio.

Figure 1 shows that, although many TBG values were within the overall reference interval (12–29 mg/L), the concentrations are significantly lower (and T3SU values significantly higher) in those who died than in those who survived. This is already apparent on admission: only four patients had TBG values similar to those who survived. In three, the values decreased before death; the changes, and the intervals between the admission and preterminal samples, were 13, 11, and 6 mg/L in two, seven, and three days, respectively. The fourth patient, who had admission and preterminal TBG values of 20 and 19 mg/L, respectively, previously had been healthy but died 9 h after an episode of cardiac arrest. In one patient the TBG concentration increased, probably as a result of massive blood transfusion. T4 concentrations in those who died were also significantly lower than in the survivors (Table 1). Again, this difference is significant in the admission samples. The FTI results are similar, but the difference in the T4/TBG ratio between fatalities and survivors is only significant for the preterminal samples.

From this, we conclude that the changes in thyroid-function tests in severely ill patients are ascribable, at least in part, to low concentrations of TBG. We do not imply from this small series that a very low TBG concentration is a sign of impending death. Although initially indistinguishable from the survivors, those who died must have been more seriously ill. Serial studies in pa-

<table>
<thead>
<tr>
<th>Table 1. Mean (and SD) for Results of Thyroid-Function Tests, and Significance of Differences in Severely Ill Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference interval</td>
</tr>
<tr>
<td>Survivors</td>
</tr>
<tr>
<td>Admission (S)</td>
</tr>
<tr>
<td>Fatalities</td>
</tr>
<tr>
<td>Admission (Fa)</td>
</tr>
<tr>
<td>Preterminal (Fp)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>S:Fa</td>
</tr>
<tr>
<td>S:Fp</td>
</tr>
<tr>
<td>Fa:Fp</td>
</tr>
</tbody>
</table>

NS, not significant.
tients currently being investigated suggest that there is a correlation between the clinical progress and TBG concentrations; improvement in the clinical condition may be accompanied by a change in the concentration of TBG toward more nearly normal.

This preliminary note documents yet another factor to be considered in interpreting T₄ values from seriously ill patients.

References


P. R. Pannall
W. R. Peisach
Janet Marshall
Sandra Stuart
C. P. Reilly
M. L. Wellby

Dept. of Clin. Chem. and
1the Intensive Therapy Unit
The Queen Elizabeth Hospital
Woodville, 5011, South Australia

Modification to the aca—A Manufacturer’s Comment That Can Be Generalized

To the Editor:

Smith et al. (1) have presented a procedure by which they take advantage of the labor-saving features of the Du Pont aca by adapting the system to handle HDL cholesterol determinations. Specifically, the HDL method of Liedtke et al. (2) is incorporated by modifying parameters of the aca pack, diluent, and instrument. Dr. Smith’s Letter is reminiscent of a previous publication by Fraser and Lindsay (3) on the adaptation of a spectrophotometric procedure for measuring total bilirubin on the aca. Both authors demonstrate a degree of flexibility in the aca system that seems bounded only by the imagination and creativity of its operators.

Nevertheless, we must caution our customers that we have not evaluated these modifications and have not designed our manufacturing quality-control procedures with such modifications in mind. Therefore, we cannot assure that all individual lots of our products will perform adequately with these modifications.

Instead, our response is to commercialize products designed to meet our customers’ needs and which are specifically designed and manufactured for the aca system. In the case of spectrophotometric total bilirubin determination, this was accomplished with the introduction of the Neonatal Bilirubin (NBIL) method in 1979. The aca High Density Lipoprotein Cholesterol (HDL) method has recently been introduced in the western United States, and worldwide commercialization is expected shortly. This method utilizes a pre-treatment step with a Du Pont-supplied buffered phosophotungstate reagent, which quantitatively precipitates low- and very-low-density lipoproteins. The high-density lipoprotein fraction is then analyzed by an enzymatic cholesterol procedure on its own unique channel. Details on this procedure, including comparison to an alternative method, will be published soon in a Field Evaluation Report. The aca HDL method eliminates the need for preparing diluent and precipitating reagents, taping of pack headers, and using existing, dedicated channels making HDL determinations available with the same degree of reliability and cost effectiveness as other aca methods.

References


Robert L. Risacher
Assistant Product Manager
Clinical Systems Division
E. I. Du Pont de Nemours & Co.
Wilmington, DE 19898

Ed. note: One reason for publishing this Letter is that the second paragraph exemplifies a commonsensical assumption that perhaps should be made specific: when modifications of a supplier’s equipment or reagents are introduced and reported in these pages, the supplier obviously is not to be held responsible (nor is this journal, for that matter) for inadequate performance of the modification. As with any other report, the prospective user must exercise his own judgment as to whether to put it to use and whether or not it appropriately and adequately meets his needs.

Lyophilization of Hemoglobin and the Stability of the Lyophylisates

To the Editor:

The recent article by Bonderman et al. (1) about the possibility of producing a freeze-dried hemoglobin control prompts us to offer some technical comments on the subject. It is entirely clear that, as Bonderman et al. observe, it would be very valuable to be able to preserve hemoglobin preparations, but that this is not possible at present, because the pigment oxidizes to methemoglobin, both in solution and during the desiccation (2–4).

The protective agent that Bonderman et al. used was sucrose, 100 g/L. This compound acts not as a cryoprotector as they indicate but as a lyoprotector, and it seems to us that this concentration is very high for a result that still could be improved—only 85% oxyhemoglobin and 15% methemoglobin. In fact, we obtained more nearly satisfactory results in 1976 (6, 7) with 0.14 mol/L (50 g/L) sucrose solution.

As Bonderman et al. indicate, other polyhydroxyl compounds are also effective. Indeed, in our laboratory satisfactory results have been obtained with many carbohydrates in concentrations not exceeding 0.25 mol/L, but also for hemoglobin solutions two or three times less concentrated. Unlike Bonderman et al., we have not obtained good results with mannitol (29% methemoglobin, in two attempts) (7). Our interest in lyoprotective agents for hemoglobin has led us to explore several chemical families which have turned out to be full of potential. Among the macromolecules, Ficolls 70 and 400 recently showed themselves very effective (8). Their probable presence in the solutions that were freeze-dried by Bonderman et al. could help to protect the hemoglobin during the desiccation, probably without those authors recognizing it. We regret not knowing the working conditions they used.

The other compounds that could contribute to the production of lyophilized controls are amine buffers such as Tris and Bis–trispropane (9); amino acids such as arginine, lysine, aspartate, and glutamate (10); and many carbohydrates (7). Other chemical families are being studied in our laboratory.

The second major point of the study we refer to was the preservation of the freeze-dried material, considered with respect to proportions of methemoglobin which in addition influence the HbO₂ saturation and the dissociation curve. These values seem high to us: 15% at the beginning of the experiment and 40% after one year or 16 months. We have experienced the same difficulty; but the figures obtained in our laboratory are much lower: <5% at time zero,