The Combined Use of CPIB and Thyroxine in Treatment of Hyperlipoproteinemias

By Edward H. Strisower, M.D., Ph.D.

ETHYL p-chlorophenoxyisobutyrate (CPIB) reliably lowers Sf 20-10^5 concentrations and thereby lowers serum triglyceride levels, but its effect on the cholesterol-rich, triglyceride-poor Sf 0-20 class is variable and of lesser magnitude. By contrast, thyroid-active substances lower predominantly the Sf 0-20 fraction and have a much smaller and less consistent effect on the Sf 20-10^5 class. Therefore, it appeared reasonable to study the effect of the combined administration of CPIB and levothyroxine in patients with the common type of generalized hyperlipoproteinemia characterized by moderate to marked elevations of both Sf 0-20 and Sf 20-10^5 levels. In addition, observations made during prolonged administration of CPIB and thyroxine on patients with Sf 0-20 hyperlipoproteinemias are discussed.

Subjects and Methods

Thirteen ambulatory patients, aged 35 to 64 years, were studied. Table 1 lists age, sex, and diagnosis of each patient. Seven patients had had a myocardial infarction; one patient had atherosclerotic heart disease and hypertension with definite electrocardiographic abnormalities, and the remainder had diagnoses as noted in table 1. Carbohydrate-sensitive hyperlipemia was defined as a hyperlipemia in which the concentration of the predominant triglyceride-bearing lipoprotein classes (Sf 20-10^5) was markedly reduced by restriction of dietary carbohydrate; one patient (case 3) had the usual associated marked impairment in carbohydrate tolerance demonstrated on repeated glucose tolerance tests. Each subject completed one or more courses of treatment with CPIB, and CPIB and thyroxine, and most were also followed while treatment with CPIB was

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>ASHD (PWI), Dupuytren's contracture, hyperuricemia</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>Hyperlipemia (carbohydrate sensitive)</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>ASHD (PWI), gout, hyperlipemia (carbohydrate sensitive), early chemical diabetes</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>M</td>
<td>ASHD (PWI)</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>F</td>
<td>ASHD (PWI), xanthoma tendinosum</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>Early chemical diabetes</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>M</td>
<td>Xanthelasma</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>M</td>
<td>ASHD (PWI)</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>M</td>
<td>ASHD (AWI, PWI)</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>M</td>
<td>Healthy</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
<td>F</td>
<td>Hysterectomy and ovariecotmy for endometriosis</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>F</td>
<td>ASHD (AWI)</td>
</tr>
<tr>
<td>13</td>
<td>55</td>
<td>M</td>
<td>ASHD, mild essential hypertension</td>
</tr>
</tbody>
</table>

ASHD = arteriosclerotic heart disease.  
PWI = old posterior wall myocardial infarction.  
AWI = old anterior wall myocardial infarction.
stopped but use of thyroxine continued. CPIB 
was given in a total daily dose of 2.0 g (0.5 g 
after breakfast and after lunch and 1.0 g after 
dinner). The dosage of levothyroxine varied from 
0.2 to 0.6 mg per day.

Each patient was followed personally at 4 to 
8-week intervals; at each visit body weight, 
pulse, and blood pressure were recorded. Each 
patient was advised to stay on a standard low 
saturated fat, low cholesterol diet as follows: 
eggs were limited to four per week; skimmed 
milk, nonfat milk, or powdered milk and their 
products were substituted for whole milk and 
cream, and their products; pork products and 
commercially prepared cold cuts, such as salami 
and liverwurst, were excluded; patients were 
further instructed to substitute corn or safflower 
seed oil or both and unsaturated margarines for 
saturated fats, such as butter, lard, and chicken 
fat. Patients were also instructed to give prefer-
ence, in order of decreasing desirability, to sea-
foods, fowl, organ meats of beef and veal (heart, 
lung, tripe), and lean cuts of beef, veal, and lamb. 
Fruits and vegetables were allowed ad libitum, 
the ingestion of nuts was encouraged, and the 
take of carbohydrate so regulated as to main-
tain constant body weight. All patients were 
otherwise on unrestricted diets and were repeatedly 
invited to maintain their diets as constant 
as possible during the entire study period. On 
this diet the change in mean group weight was 
less than 1 pound.

Serum lipoprotein analyses after the differenti-
.al gradient ultracentrifuge method of de Lalla 
and Gofman3 or by high precision refractometry 
utilizing the method of Lindgren and associ-
ates4 or by both, were done at 4 to 8-week in-
tervals on all patients' serums before any drug was 
given, during administration of CPIB, CPIB and 
levothyroxine, and of thyroxine without CPIB, 
and during suitable control periods when no 
medication was given. The refractometric and 
analytic ultracentrifugal methods gave practically 
identical results for the major low density Sf 
0-20 and Sf 20-105 lipoprotein classes in a large 
series of replicate analyses. In addition to serial 
lipoprotein measurements, blood cholesterol was 
measured, and routine complete blood counts, 
urinalyses, and other clinical laboratory tests were 
obtained as needed for the exclusion of untoward 
side effects of drug therapy.

The period of study varied with each individ-
ual patient but ranged from 58 to 201 weeks, 
and the mean observation period for the group 
was 104 weeks.

Results and Discussion

As has been noted before, the responses of 
the two major low density lipoprotein 
classes, Sf 0-20 and Sf 20-105, to CPIB were 
qualitatively and quantitatively different.1 
The concentration of lipoprotein in the Sf 
20-105 class is lowered sharply by CPIB. This 
effect was found to be quite consistent in all 
13 patients in the present study and did not 
appear to depend on the initial lipoprotein 
pattern. Mean lowering in the Sf 20-105 class 
was 55%, and the addition of levothyroxine 
(T-4) to the CPIB regimen did not produce 
any further change in concentration (table 2).

By contrast, the Sf 0-20 response to CPIB 
was found to be variable, ranging from a 270% 
increase to a 35% decrease of the initial con-
centration. It became of interest to determine 
whether this variable Sf 0-20 response is re-
lated to the initial lipoprotein pattern. The 
13 patients, therefore, were classified into one 
of three subgroups: (1) seven patients in whom 
Sf 0-20 hyperlipoproteinemia was the 
predominant lipid abnormality, (2) four pa-
tients with combined Sf 0-20 and Sf 20-105 
hyperlipoproteinemia (table 3), and (3) two 
patients with carbohydrate-sensitive hyper-
lipemias characterized by massively elevated 
Sf 20-105 concentrations (tables 4 and 5). 
(Patient 3 also had subnormal Sf 0-20 con-
centration.) Tables 3, 4, and 5 summarize the 
Sf 0-20 response to CPIB and CPIB and T-4 
obtained in these three subgroups with dif-
ferent initial lipoprotein distributions.

Table 2

<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>Pretreatment concentration</th>
<th>On CPIB Concentration</th>
<th>% change</th>
<th>On CPIB + T-4 Concentration</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sf 0-20</td>
<td>641</td>
<td>654</td>
<td>+ 2.0</td>
<td>563</td>
<td>-13.9</td>
</tr>
<tr>
<td>Sf 20-105</td>
<td>509</td>
<td>229</td>
<td>-55.0</td>
<td>232</td>
<td>+ 1.3</td>
</tr>
</tbody>
</table>

All concentrations are expressed in mg/100 ml of serum.

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### Table 3

**Relation of Drug Response to Initial Lipoprotein Pattern**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Type of hyperlipoproteinemia</th>
<th>Mean initial lipoprotein concentration 0-20</th>
<th>Effect of CPIB 0-20</th>
<th>*Effect of CPIB + T-4 0-20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pt. N.V.</td>
<td>20-106</td>
<td>Pt. N.V.</td>
<td>20-106</td>
</tr>
<tr>
<td>5</td>
<td>0-20 (a)</td>
<td>713</td>
<td>430</td>
<td>155</td>
</tr>
<tr>
<td>2</td>
<td>0-20 (b)</td>
<td>877</td>
<td>433</td>
<td>188</td>
</tr>
<tr>
<td>4</td>
<td>(0-20)+(20-106)</td>
<td>590</td>
<td>457</td>
<td>471</td>
</tr>
</tbody>
</table>

*Data recorded in last two columns represent further changes observed on addition of T-4 to treatment of patients already receiving CPIB.

†figure representing drug-induced lipoprotein concentration changes is statistically significant (P < 0.05 or < 0.01).

N.V. = normal control values in individuals matched by age and sex.

Lipoprotein concentrations are expressed in mg/100 ml of serum; 0-20 and 20-106 represent lipoprotein classes usually expressed as Sf 0-20 and Sf 20-106; a and b are subgroups.

### Table 4

**Mean Serum Lipoprotein Concentrations in a Patient with Carbohydrate-Sensitive Hyperlipoproteinemia Associated with Early Chemical Diabetes, Gout, and Old Posterior Wall Myocardial Infarction (Patient 3, 45-year-old White Man)**

<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>N.V.</th>
<th>No treatment (1 wk)</th>
<th>CPIB (36 wk)</th>
<th>CPIB + T-4 (64 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sf 0-20</td>
<td>437</td>
<td>249 (1)</td>
<td>673 (7)</td>
<td>600 (8)</td>
</tr>
<tr>
<td>Sf 20-106</td>
<td>173</td>
<td>1967 (1)</td>
<td>887 (7)</td>
<td>973 (8)</td>
</tr>
<tr>
<td>CS</td>
<td>240</td>
<td>442</td>
<td>410</td>
<td>403</td>
</tr>
</tbody>
</table>

N.V. = normal control values in healthy age and sex matched individuals.

Numbers in parentheses refer to number of samples.

Lipoprotein concentrations are expressed in mg/100 ml of serum.

CS = cholesterol, mg/100 ml of serum.

### Table 5

**Mean Serum Lipoprotein Concentrations in a Patient with Carbohydrate-Induced Hyperlipoproteinemia (Patient 2, 37-year-old White Man)**

<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>N.V.</th>
<th>No treatment (31 wk)</th>
<th>CPIB (21 wk)</th>
<th>CPIB + T-4 (35 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sf 0-20</td>
<td>416</td>
<td>422 (5)</td>
<td>934 (3)</td>
<td>729 (2)</td>
</tr>
<tr>
<td>Sf 20-106</td>
<td>168</td>
<td>1635 (5)</td>
<td>734 (3)</td>
<td>786 (2)</td>
</tr>
<tr>
<td>CS</td>
<td>232</td>
<td>430 (4)</td>
<td>431 (3)</td>
<td>357 (2)</td>
</tr>
</tbody>
</table>

N.V. = normal control values in healthy age and sex matched subjects.

Numbers in parentheses refer to number of samples.

Lipoprotein concentrations are expressed in mg/100 ml of serum.

CS = cholesterol, mg/100 ml of serum.

Five of the seven patients in group 1 (identified as Sf 0-20 [a] in table 3) showed no significant over-all changes in Sf 0-20 levels when given CPIB (the 8% reduction is not statistically significant). Two patients (cases 7 and 11, identified as Sf 0-20 [b] in table 3), however, responded with a marked and highly significant 36% reduction in their Sf 0-20 concentration when given CPIB. This unusual effect of CPIB is described in detail later. When T-4 was added to the CPIB regimen, a moderate but consistent Sf 0-20 reduction occurred in all seven patients (mean decrease was 11%).

In the four patients with combined Sf 0-20 and Sf 20-106 hyperlipoproteinemia, CPIB...
had no statistically significant effect on Sf 0-20 concentrations though a slight tendency for this lipoprotein class to rise was noted; the group mean Sf 0-20 rise was 5%. Addition of T-4 again resulted in a moderate but consistent Sf 0-20 decrease (mean reduction 17%, P < 0.01).

Table 4 summarizes the lipoprotein changes observed in patient 3 with carbohydrate-sensitive hyperlipemia and early chemical diabetes mellitus with normal fasting blood sugar levels, during an observation period of 101 weeks. The large increase in Sf 0-20 concentration accompanying the expected Sf 20-10^5 reduction produced by CPIB is noteworthy. It is also apparent that addition of T-4 did not affect the CPIB-induced Sf 0-20 hyperlipoproteinemia significantly; nor is the slight Sf 20-10^5 rise noted during the CPIB and T-4 phase statistically significant. Very similar CPIB-induced changes in lipoprotein concentrations were observed in patient 2, another patient with carbohydrate-sensitive hyperlipemia (table 5). Sf 0-20 concentration increases have been noted previously in two other patients with carbohydrate-sensitive hyperlipemia and gout treated with CPIB.1

It, therefore, appears likely that the marked Sf 0-20 elevation represents a pharmacological effect of CPIB in patients with this type of hyperlipoproteinemia.

The unusual Sf 0-20 lowering effect of CPIB in patient 7 with Sf 0-20 hyperlipoproteinemia is illustrated in figure 1 which shows lipoprotein changes induced by dextrothyroxine, a combination of 97.5% CPIB and 2.5% androsterone (Atromid), and by CPIB, CPIB and levothyroxine, and levothyroxine used separately in a healthy 45 year-old man with xanthelasma observed for more than 3 years. Figure 1 illustrates a number of interesting pharmacological effects on serum lipoprotein concentrations as follows: (1) The typical Sf 0-20 reduction produced by dextrothyroxine, followed by the usual rebound effect when use of this drug was stopped, occurred with a lesser Sf 20-10^5 reduction and rebound as observed in previous studies.2, 5, 6 (2) A prompt and marked reduction in Sf 0-20 levels occurred when Atromid or CPIB was ingested. The similarity of this response to that obtained with dextrothyroxine was striking. The usual Sf 20-10^5 reduction induced by CPIB was also present. (3) The addition of T-4 to the CPIB regimen seemed to cause a moderate further Sf 0-20 lowering (from 623 to 483 mg/100 ml) at approximately 120 to 135 weeks of study but did not cause any significant further changes in Sf 20-10^5 levels. (4) When CPIB was discontinued, but T-4 continued, a rise in Sf 0-20 concentration occurred, indicating again that in this patient CPIB had a definite Sf 0-20 lowering effect; the Sf 20-10^5 concentration fluctuated markedly, but a trend is discernible that suggests a rebound effect due to CPIB withdrawal.

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Figure 2 shows a longitudinal profile of lipoprotein changes in the other patient (no. 11), with an Sf 0-20 hyperlipoproteinemia, who showed marked Sf 0-20 reduction as a result of CPIB administration. The marked Sf 20-10<sup>5</sup> reduction, even though initial concentrations were normal, is also noteworthy. In spite of the usual Sf 0-20 lowering action of thyroid-active substances, in this patient 0.4 mg daily of levothyroxine did not maintain the reduction of Sf 0-20 concentration achieved with CPIB. The expected Sf 20-10<sup>6</sup> rise on CPIB withdrawal (rebound effect) was also noted. Whether or not the estrogenic preparation (Premarin) given throughout the entire period of study had any effect on the “atypical” Sf 0-20 lowering effect of CPIB in this patient cannot be determined from our data. However, the data obtained on patient 7 (fig. 1) demonstrate that at least in a male subject a profound CPIB-induced Sf 0-20 reduction can occur without concurrent estrogen administration. The incidence of CPIB-responsive Sf 0-20 hyperlipoproteinemias can not be determined from the data herein presented. In this author’s experience only seven of 44 patients have responded to CPIB with Sf 0-20 lowering of 25% or more, an incidence of 16%. The physiological and biochemical reasons for this pharmacological effect of CPIB are unknown.

**Conclusions**

Whereas the response of the Sf 20-10<sup>5</sup> class to CPIB is rather uniform and does not seem to depend significantly on the initial lipoprotein pattern of the patient, the Sf 0-20 response to CPIB varies greatly. Thus, in five patients with Sf 0-20 hyperlipoproteinemias, the Sf 0-20 class was not affected by CPIB, yet a substantial decrease (averaging 36 per cent) in this class occurred in two other patients. On the other hand, the Sf 0-20 concentration rose by 270% in one patient (no. 3) with carbohydrate-sensitive hyperlipemia pattern (low Sf 0-20 and high Sf 20-10<sup>6</sup> concentrations). In general, the addition of thyroid-active substances caused a decrease in Sf 0-20 levels regardless of what effect CPIB had on this lipoprotein class, but had no further effect on Sf 20-10<sup>6</sup> levels previously reduced by CPIB.

The variability of the Sf 0-20 response to CPIB is so great that meaningful interpretations cannot be based on mean group changes in lipoprotein concentrations derived from a small series of 13 patients with different initial lipoprotein patterns. Analysis of lipoprotein concentration changes induced by single and combined administration of CPIB and thyroid-active substances was made, therefore, in terms of categories of initial lipoprotein patterns.

**Summary**

The combined effect of CPIB and levothyroxine on lipoprotein concentrations in 13 patients with various types of hyperlipoproteinemias has been investigated. Analysis of long-
term observations indicates the following: (1) CPIB lowers Sf 20-10^5 concentrations profoundly regardless of the initial lipoprotein distribution. (2) Addition of levothyroxine to CPIB produces no further significant effect on Sf 20-10^5 concentrations. (3) The effect of CPIB on Sf 0-20 concentrations appears to depend on the initial lipoprotein distribution. In carbohydrate-sensitive hyperlipoproteinemias CPIB can markedly increase Sf 0-20 levels, whereas it has no such effect in other hyperlipoproteinemias. On occasion, a marked Sf 0-20 lowering effect occurs in patients with Sf 0-20 hyperlipoproteinemias. Two such instances are reported in detail. (4) In combined Sf 0-20 and Sf 20-10^5 hyperlipoproteinemias the combination of CPIB and thyroxine is often more effective than either agent used separately in reducing total lipoprotein concentrations.

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References


An Eighteenth Century Cleric's Praise of Certain Physicians

Yet ... from time to time, some lovers of mankind ... have endeavoured (even contrary to their own interest) to reduce physic to its ancient standard: ... Even in the last age there was something of this kind done, particularly by the great and good Dr. Sydenham: and in the present, by his pupil Dr. Dover, who has pointed out simple medicines for many diseases. And some such may be found in the writings of the learned and ingenious Dr. Cheyne: who doubtless would have communicated many more to the world, but for the melancholy reason he gave one of his friends, that prest him with some passages in his works, which too much countenanced the modern practise, "O Sir, we must do something to oblige the Faculty, or they will tear us in pieces." —John Wesley. Primitive Physic. London, The Epworth Press, 1960, p. 27.
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