Mode of Action of Chlorophenoxyisobutyric Acid on Cholesterol Metabolism in Man

By L. Horlick, M.D., B. J. Kudchodkar, M. Sc., and H. S. Sodhi, M.D., Ph.D.

SUMMARY

In short-term trials chlorophenoxyisobutyric acid (CPIB) (Atromid-S) reduced the plasma cholesterol and triglyceride levels in eight subjects with type II and IV hyperlipidemias to an equal extent. In these subjects, who were maintained on constant solid food diets, CPIB administration resulted in increased excretion of fecal neutral and acidic sterols in the type II subjects only. There was an immediate increase in specific activity of plasma cholesterol in seven of the eight subjects, and a reduced rate of fall of specific activity in many of the subjects. It is suggested that CPIB inhibits the synthesis of cholesterol in vivo, and that the subsequent fall in plasma cholesterol is responsible for the release of cholesterol with higher specific activity from tissues into the plasma pool.

Additional Indexing Words:
Atromid-S Plasma cholesterol
Fecal neutral and acidic steroids Mobilization of tissue cholesterol
Plasma triglycerides Specific activity Inhibition of synthesis

CHLOROPHENOXYISOBUTYRIC acid (CPIB) has been found to be an effective drug in the treatment of hyperlipidemias characterized by increases in cholesterol and triglycerides (type IV of Frederickson’s classification), and of limited value in the treatment of hypercholesterolemia without elevated triglycerides (type II). Its mode of action in man is not well understood. Avoy et al. reported that CPIB inhibited cholesterol biosynthesis in rat livers at a stage between acetate and mevalonate. Nestel et al. noted a decrease in the rate of fall of specific activity of plasma cholesterol during treatment with CPIB in man, and suggested that this decrease could be explained on the basis of reduced synthesis of cholesterol with reduced dilution of the labeled pool. Recently Grundy et al. reported that, in hyperlipidemic patients, the drug caused an increase in excretion of cholesterol and its metabolites in the feces.

We wish to report on the effect of short-term treatment with CPIB on cholesterol metabolism in individuals with type II and type IV hyperlipidemia.

Methods

We studied subjects with hyperlipidemia and/or coronary heart disease (table 1). Two subjects, L.H. (type II) and P.P. (type IV), had periorbital xanthelasma. There were no subjects with tendon xanthomas. The patients were classified into appropriate lipoprotein types according to Frederickson et al. Three subjects were classified as type II, and four as type IV. One subject, S.J., with a history of myocardial infarction, had normal serum lipids at the time of the study. The subjects consumed a natural food diet of constant composition which resembled their habitual diet and was designed to be adequate in calories to maintain weight. The composition of the diets is given in table 2. The diet was prepared from a single pool of food. Sufficient daily servings were prepared and frozen to last for the duration of the entire study. A trial
### Table 1

**Clinical Data for Patients Studied**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical diagnosis</th>
<th>Period of clinical observation (yr)</th>
<th>% of normal weight*</th>
<th>Plasma cholesterol (range and median) (mg/100 ml)</th>
<th>Triglycerides (range and median) (mg/100 ml)</th>
<th>Hyperlipidemia type</th>
</tr>
</thead>
<tbody>
<tr>
<td>F.G.</td>
<td>F</td>
<td>48</td>
<td>F.H. of premature CHD</td>
<td>4</td>
<td>90.7</td>
<td>258 – 328</td>
<td>64</td>
<td>II</td>
</tr>
<tr>
<td>H.P.</td>
<td>M</td>
<td>32</td>
<td>Angina, F.H. of CHD</td>
<td>2</td>
<td>101.4</td>
<td>280 – 394</td>
<td>41 – 205</td>
<td>II</td>
</tr>
<tr>
<td>L.H.</td>
<td>F</td>
<td>37</td>
<td>Xanthelasma, F.H. of CHD</td>
<td>5</td>
<td>114.0</td>
<td>285 – 560</td>
<td>65 – 115</td>
<td>II</td>
</tr>
<tr>
<td>S.J.</td>
<td>M</td>
<td>51</td>
<td>CHD (myocardial infarction)</td>
<td>1</td>
<td>103.8</td>
<td>200 – 267</td>
<td>80 – 210</td>
<td>N</td>
</tr>
<tr>
<td>A.M.</td>
<td>M</td>
<td>46</td>
<td>CHD (angina)</td>
<td>2</td>
<td>119.1</td>
<td>200 – 284</td>
<td>250 – 270</td>
<td>IV</td>
</tr>
<tr>
<td>T.R.</td>
<td>M</td>
<td>44</td>
<td>Venous insufficiency, pulmonary infarction</td>
<td>1</td>
<td>148.5</td>
<td>212 – 415</td>
<td>233 – 663</td>
<td>IV</td>
</tr>
<tr>
<td>P.B.</td>
<td>M</td>
<td>36</td>
<td>Xanthelasma, CHD</td>
<td>2</td>
<td>108</td>
<td>204 – 344</td>
<td>111 – 290</td>
<td>IV</td>
</tr>
</tbody>
</table>

Abbreviations: CHD = coronary heart disease; F.H. = family history; N = normal.

*Calculated as \( \frac{\text{weight in kg}}{\text{height in cm}} \times 100 \).
period of 7 days was allowed in order that the patients might become accustomed to the diet and corrections for weight changes might be made. Whole daily diets were homogenized and extracted with organic solvents for determination of their cholesterol and plant sterol content. The natural food diet, although more difficult to prepare and control than formula diets, was preferred because it would not disturb gastrointestinal flora or motility. Chromic oxide (100 mg t.i.d.) was given with meals for correction of variations in stool flow.

Fifty μCi of 4-14C-cholesterol, dissolved in 1 ml ethanol and dispersed in 150 ml saline, was administered intravenously. We then allowed 3 to 4 weeks to elapse prior to sample collection, in order to permit equilibration of radioactive cholesterol between plasma lipoproteins and other body pools, and to permit equilibration of specific activity (SA) of bile and fecal metabolites of plasma cholesterol.

4-14C-cholesterol was injected on day 0 of the experiment. Administration of the constant natural food diet and of chromic oxide was begun on day 21. Control periods were (a) an initial dietary equilibration period of 7 days, followed by (b) a control period (no drug treatment) of 12 to 15 days, followed by (c) a treatment period of 12 to 15 days during which CPIB (500 mg q.i.d.) was administered. Blood samples were drawn from patients in the fasting state two or three times a week. Aliquots of plasma were extracted with chloroform-methanol and washed. The lipid extract was evaporated almost to dryness, dissolved in chloroform, and subjected to thin layer chromatography in ether-hexane-glacial acetic acid (15:85:1.5). Free and esterified cholesterol and triglyceride were eluted from the silicic acid with ether. Triglycerides were determined by an autoanalyzer technique. Aliquots of free and esterified cholesterol were taken for determination of radioactivity (in a liquid scintillation spectrometer) and mass (by the ferric chloride method).

Feces were collected in weighed cans in 3-day pools, beginning with the control period. They were weighed, diluted with an equal weight of water, and homogenized by shaking for 3 min on a paint shaker. Aliquots were removed for extraction of neutral and acidic sterols by the methods of Miettinen et al. and Grundy et al. The extracts were decolorized by heating with hydrogen peroxide, and were then evaporated and dissolved in scintillation mixture (PPO-POPOP-toluene). Radioactivity was determined in a liquid scintillation spectrometer (Packard, Tri-Carb, Model 3003), and the counts were corrected for quenching by the use of an external standard.

The total amount of radioactivity in the fecal neutral and acidic fractions was divided by the SA of plasma cholesterol at the start of the collection period in order that the mass of neutral and acidic sterols arising from the plasma cholesterol pool might be obtained. The results obtained were corrected for stool flow and losses by determination of the chromic oxide content per gram of fecal emulsion.

### Table 2

**Composition of Mixed Natural Food Diets**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type of hyperlipidemia</th>
<th>Total no. calories</th>
<th>Protein (%)</th>
<th>Fat (%)</th>
<th>Carbohydrate (%)</th>
<th>Cholesterol (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F.G.</td>
<td>II</td>
<td>2150</td>
<td>11.3</td>
<td>39.8</td>
<td>48.9</td>
<td>401</td>
</tr>
<tr>
<td>H.P.</td>
<td>II</td>
<td>1954</td>
<td>31.3</td>
<td>22.4</td>
<td>46.3</td>
<td>659</td>
</tr>
<tr>
<td>L.H.</td>
<td>II</td>
<td>1003</td>
<td>25.9</td>
<td>27.8</td>
<td>46.4</td>
<td>594</td>
</tr>
<tr>
<td>S.J.</td>
<td>N</td>
<td>2265</td>
<td>13.9</td>
<td>21.6</td>
<td>64.5</td>
<td>1100</td>
</tr>
<tr>
<td>A.M.</td>
<td>IV</td>
<td>2327</td>
<td>18.9</td>
<td>26.9</td>
<td>54.2</td>
<td>575</td>
</tr>
<tr>
<td>T.R.</td>
<td>IV</td>
<td>1696</td>
<td>25.7</td>
<td>42.4</td>
<td>31.9</td>
<td>1214</td>
</tr>
<tr>
<td>P.P.</td>
<td>IV</td>
<td>2133</td>
<td>18.9</td>
<td>39.3</td>
<td>41.8</td>
<td>564</td>
</tr>
<tr>
<td>P.B.</td>
<td>IV</td>
<td>1945</td>
<td>18.2</td>
<td>48.7</td>
<td>33.1</td>
<td>1190</td>
</tr>
</tbody>
</table>

Daily excretion of endogenous fecal neutral sterols (mg/day)

\[
\text{Daily excretion} = \frac{\text{total radioactivity in neutral steroid fraction (dpm/day)}}{\text{SA of plasma cholesterol (dpm/mg) 2 days previously}}
\]

Daily excretion of endogenous fecal acidic sterols (mg/day)

\[
\text{Daily excretion} = \frac{\text{total radioactivity in acidic steroid fraction (dpm/day)}}{\text{SA of plasma cholesterol (dpm/mg) 2 days previously}}
\]
Grundy et al.\textsuperscript{14} have demonstrated that the steroid nucleus may be degraded during its passage through the gastrointestinal tract, and that the amount degraded is highly variable between individuals, but quite consistent for each individual. Corrections may be made by measure-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Effect of CPIB on free and esterified cholesterol in type II and type IV hyperlipemias. The right-hand panel summarizes the results for free and esterified cholesterol in all subjects regardless of type.}
\end{figure}

\begin{table}[h]
\centering
\caption{Effect of CPIB on Serum Lipids in Types II and IV Hyperlipidemia}
\begin{tabular}{llllll}
\hline
Patient & Type & Treatment* & Cholesterol† & & & \\
& & & Free (mg/100 ml) & Ester (mg/100 ml) & Total (mg/100 ml) & Triglyceride (mg/100 ml) \\
\hline
F.G. & II & None (9;4) & 84 ± 2 & 196 ± 5 & 279 ± 7 & 94 ± 4 \\
& & CPIB (15;4) & 74 ± 3 & 167 ± 4 & 244 ± 5\textsuperscript{t} & 70 ± 4\textsuperscript{t} \\
& & None (12;2) & 83 ± 4 & 168 ± 19 & 251 ± 11 & 100 ± 14 \\
& & None (12;4) & 91 ± 2 & 206 ± 1 & 293 ± 4 & 159 ± 9 \\
H.P. & II & CPIB (12;4) & 76 ± 2 & 160 ± 3 & 237 ± 4\textsuperscript{t} & 111 ± 5\textsuperscript{t} \\
& & None (9;4) & 154 ± 14 & 276 ± 7 & 431 ± 21 & 112 ± 9 \\
L.H. & II & CPIB (12;4) & 113 ± 7 & 226 ± 27 & 339 ± 33\textsuperscript{t} & 83 ± 6\textsuperscript{t} \\
& & None (12;4) & 77 ± 8 & 206 ± 5 & 284 ± 13 & 163 ± 12 \\
S.J. & N & CPIB (12;4) & 46 ± 7 & 182 ± 18 & 227 ± 23\textsuperscript{t} & 98 ± 19\textsuperscript{t} \\
& & None (12;4) & 68 ± 2 & 159 ± 2 & 224 ± 1 & 283 ± 17 \\
A.M. & IV & CPIB (15;4) & 56 ± 3 & 142 ± 7 & 198 ± 7\textsuperscript{t} & 147 ± 17\textsuperscript{t} \\
& & CPIB and low calorie diet (12;3) & 48 ± 2 & 116 ± 4 & 163 ± 8 & 95 ± 3\textsuperscript{t} \\
& & None (9;4) & 104 ± 3 & 252 ± 6 & 356 ± 8 & 333 ± 24 \\
T.R. & IV & CPIB (15;4) & 86 ± 9 & 218 ± 22 & 301 ± 31\textsuperscript{t} & 246 ± 69\textsuperscript{§} \\
& & None (9;4) & 81 ± 2 & 206 ± 5 & 287 ± 5 & 388 ± 193 \\
& & None (9;4) & 81 ± 4 & 201 ± 7 & 282 ± 10 & 137 ± 5 \\
P.P. & IV & CPIB (18;4) & 65 ± 7 & 175 ± 16 & 241 ± 24\textsuperscript{t} & 111 ± 8\textsuperscript{§} \\
& & None (9;4) & 65 ± 6 & 171 ± 4 & 235 ± 10 & 146 ± 19 \\
& & None (9;4) & 78 ± 6 & 165 ± 8 & 246 ± 14 & 284 ± 12 \\
P.B. & IV & CPIB (18;4) & 68 ± 4 & 134 ± 9 & 203 ± 26\textsuperscript{t} & 153 ± 41\textsuperscript{t} \\
\hline
\end{tabular}
\textsuperscript{*Duration of balance period (days) and number of blood samples analyzed.}
\textsuperscript{†±SD.}
\textsuperscript{tP < 0.01.}
\textsuperscript{§P < 0.02.}
\end{table}
Table 4

Effect of CPIB on Fecal Sterols in Types II and IV

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type</th>
<th>Treatment*</th>
<th>Neutral sterols (mg/day)†</th>
<th>Acidic sterols (mg/day)†</th>
<th>Total sterols (mg/day)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>F.G. II</td>
<td>None</td>
<td>(9:3)</td>
<td>155 ± 7</td>
<td>94 ± 8</td>
<td>250 ± 13</td>
</tr>
<tr>
<td>CPIB</td>
<td>(15:5)</td>
<td></td>
<td>277 ± 18</td>
<td>178 ± 25</td>
<td>455 ± 11</td>
</tr>
<tr>
<td>None</td>
<td>(12:4)</td>
<td></td>
<td>160 ± 10</td>
<td>73 ± 12</td>
<td>232 ± 16</td>
</tr>
<tr>
<td>H.P. II</td>
<td>None</td>
<td>(12:4)</td>
<td>333 ± 44</td>
<td>326 ± 26</td>
<td>659 ± 69</td>
</tr>
<tr>
<td>CPIB</td>
<td>(12:4)</td>
<td></td>
<td>569 ± 42</td>
<td>554 ± 46</td>
<td>1119 ± 264</td>
</tr>
<tr>
<td>None</td>
<td>(9:3)</td>
<td></td>
<td>331 ± 103</td>
<td>228 ± 81</td>
<td>559 ± 180</td>
</tr>
<tr>
<td>L.H. II</td>
<td>None</td>
<td>(12:4)</td>
<td>705 ± 89</td>
<td>385 ± 40</td>
<td>1056 ± 76</td>
</tr>
<tr>
<td>CPIB</td>
<td>(12:4)</td>
<td></td>
<td>473 ± 35</td>
<td>358 ± 20</td>
<td>830 ± 45</td>
</tr>
<tr>
<td>None</td>
<td>(12:4)</td>
<td></td>
<td>472 ± 35</td>
<td>358 ± 20</td>
<td>830 ± 45</td>
</tr>
<tr>
<td>S.J. N</td>
<td>None</td>
<td>(12:4)</td>
<td>412 ± 10</td>
<td>135 ± 7</td>
<td>547 ± 24</td>
</tr>
<tr>
<td>CPIB</td>
<td>(12:4)</td>
<td></td>
<td>792 ± 240</td>
<td>333 ± 33</td>
<td>1125 ± 235</td>
</tr>
<tr>
<td>A.M. IV</td>
<td>CPIB</td>
<td>(15:5)</td>
<td>431 ± 21</td>
<td>103 ± 9</td>
<td>544 ± 33</td>
</tr>
<tr>
<td>None</td>
<td>(12:4)</td>
<td></td>
<td>522 ± 11</td>
<td>48 ± 10</td>
<td>569 ± 14</td>
</tr>
<tr>
<td>T.R. IV</td>
<td>None</td>
<td>(9:3)</td>
<td>600 ± 18</td>
<td>307 ± 90</td>
<td>908 ± 72</td>
</tr>
<tr>
<td>CPIB</td>
<td>(15:5)</td>
<td></td>
<td>572 ± 35</td>
<td>333 ± 63</td>
<td>925 ± 49</td>
</tr>
<tr>
<td>None</td>
<td>(9:3)</td>
<td></td>
<td>573 ± 33</td>
<td>361 ± 48</td>
<td>935 ± 102</td>
</tr>
<tr>
<td>P.P. IV</td>
<td>CPIB</td>
<td>(18:6)</td>
<td>434 ± 62</td>
<td>345 ± 24</td>
<td>778 ± 71</td>
</tr>
<tr>
<td>None</td>
<td>(9:3)</td>
<td></td>
<td>386 ± 25</td>
<td>338 ± 68</td>
<td>724 ± 43</td>
</tr>
<tr>
<td>None</td>
<td>(9:3)</td>
<td></td>
<td>537 ± 32</td>
<td>293 ± 67</td>
<td>830 ± 83</td>
</tr>
<tr>
<td>P.B. IV</td>
<td>CPIB</td>
<td>(15:5)</td>
<td>488 ± 52</td>
<td>259 ± 56</td>
<td>799 ± 65</td>
</tr>
</tbody>
</table>

Abbreviation: ns = not significant.
*Duration of balance period (days) and number of blood samples analyzed.
†±SD.

The fall of treatment. The reduction in serum cholesterol levels was apparent in the first blood samples drawn 2 to 5 days after treatment was begun, and the levels stabilized at 15 to 20 days of treatment. The reduction in serum lipids during the treatment period was essentially similar in both types II and IV, and is shown in table 3. The effects of stoppage of treatment with CPIB were studied in one type II subject (F.G.) and in two type IV subjects (T.R. and P.P.). In all three, the cholesterol remained low during the period of observation (12–15 days), whereas the triglycerides promptly returned to pretreatment levels. Later measurements showed a slow return of cholesterol to pretreatment levels. The addition of a low calorie diet to CPIB treatment in one type IV subject (A.M.) resulted in a further fall in plasma cholesterol and triglycerides. One subject in the type IV group (P.P.), whose pretreatment triglyceride levels ranged between 729 and 209 mg/100 ml over a 1-year period, showed a fall in his triglyceride levels when placed on the equicaloric constant diet (dietary equilibration period). This decrease was apparently due to a slight weight loss resulting from an underes-
timate of his caloric needs. Despite this initial fall, his triglyceride levels fell further when CPIB treatment was begun.

**Fecal Neutral and Acidic Sterols**

*(Table 4 and Figures 2-9)*

The three type II subjects and the single subject with normal lipids showed a consistent increase in the excretion of fecal neutral sterols during the treatment period. Three out of four also showed an increased excretion of acidic sterols. In one subject (F.G.), cessation of treatment resulted in a prompt return to pretreatment levels. Type IV subjects showed no changes in fecal neutral or acidic sterols during treatment, although one subject (A.M.) showed an increase in neutral sterols and a decrease in acidic sterols when a low calorie diet was added to the CPIB treatment. Examination of the control period data indicates that type II subjects tended to excrete smaller amounts of fecal neutral and acidic sterols than type IV subjects.

**Specific Activity of Plasma Cholesterol**

*(Figures 2–9)*

The curves of SA of plasma cholesterol became exponential 3 to 4 weeks after

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**Figures 2–9**

*Effect of CPIB on free and esterified cholesterol, triglycerides, body weight, serum cholesterol specific activity, and excretion of fecal neutral and acidic sterols. Arrows indicate days on which the constant diet and treatment (CPIB) were begun. Day 0 is the date of administration of 4-14C-cholesterol. The bars indicating fecal neutral and acidic sterols are superimposed on one another and are not additive. Figures 2, 3, and 4 are type II, figure 5 is normolipidemic, and figures 6, 7, 8, and 9 are type IV.*

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injection of $^{14}$C-cholesterol, and before the control studies were begun. The slopes of the curves of SA of plasma free and esterified cholesterol were parallel, but the SA of esterified cholesterol was greater than that of free cholesterol in most instances. Treatment with CPIB did not alter the ratio of free to esterified cholesterol. However, as soon as treatment was begun there was a prompt increase in the SA of both cholesterol fractions in seven of the eight subjects studied. This change was noted in the first determination made 48–72 hr after treatment was begun. Two patients in each group also showed a flattening, or reduced rate of fall, of the SA curve subsequent to the initial rises.

**Discussion**

These results relate to relatively short-term effects of CPIB treatment. During the brief treatment period (12–15 days) there were significant reductions in plasma lipids in both types II and IV subjects. Short-term reductions in plasma lipids in types II and IV subjects may be due to a variety of factors, including changes in dietary intake, changes in drug absorption, or changes in cellular metabolism.

In order to be certain that these changes in the curve of SA of plasma cholesterol were not an artifact due to the rather unphysiological method of administering the $^{14}$C-cholesterol, we administered a separate dose of $^3$H-cholesterol orally to a subject (L.H.) who had already received $^{14}$C-cholesterol intravenously. The curves of SA of plasma cholesterol ($^{14}$C and $^3$H) both showed the initial rise in SA (fig. 4).
subjects treated with CPIB have been reported by many observers, but there is conflict of opinion regarding the long-term results with type II subjects. Treatment with CPIB resulted in increased excretion of fecal neutral sterols and bile acids in the type II but not in the type IV subjects. Grundy et al. found that CPIB produced significant increases in fecal excretion of endogenous neutral sterols in 15 normo- and hyperlipoproteinemic patients, but it is not clear from their abstract whether this was true of all the lipoprotein types (I–V) studied. We know of no other observations such as ours, reporting a difference in response of type II and type IV patients. There is reason to believe that these two classes of hyperlipidemia represent fundamentally different disorders, and that they might respond differently to the drug. Thus the diabetic diathesis is rare in type II, but common in type IV patients. The type IV patient is very sensitive to weight restriction and, to a lesser degree, to restriction of simple sugars in the diet, whereas the type II patient is unaffected by these measures. Kottke recently demonstrated much larger cholic acid pools and greater daily turnover of cholic and chenodeoxycholic acids in type IV than in type II patients. An alternate explanation for the difference in response of types II and IV subjects to CPIB (with respect to fecal neutral and acidic

Figure 6

Figure 7
CPIB AND CHOLESTEROL METABOLISM

Figure 8

sterols) could be the following. Three of the four subjects with type IV had only modest cholesterol elevations in the plasma. This could indicate that these subjects had little or no excess cholesterol stored in their depots to be fluxed out of the body with administration of CPIB. More subjects with higher plasma levels of cholesterol (and presumably larger body stores of cholesterol) will have to be studied before this problem can be resolved.

There were early (within 2–3 days of starting treatment) rises in the SA curve of plasma cholesterol, with subsequent flattening or reduction in rate of decline of the SA curve, in some individuals in both groups. These early changes in specific activity were associated with relatively small changes in the plasma cholesterol levels. Flattening or reduced rate of fall of the SA curve of plasma cholesterol may be due to (a) reduction in synthesis of cholesterol with reduced entry into and reduced dilution of the labeled pool, or (b) decreased absorption of exogenous cholesterol, or (c) both. The immediate rise in specific activity, however, can only be explained as due to an influx of highly labeled cholesterol from a site other than the liver plasma pool. A continued influx of highly labeled cholesterol could also be responsible for the flattening or reduced rate of fall of the SA curve. Similar results have been reported by Miettinen,20,21 using a variety of techniques for lowering plasma cholesterol, such as administration of nicotinic acid and weight reduction. In each instance, there was an early rise in the SA curve of plasma cholesterol associated with minor changes in plasma cholesterol. Grundy et al.4 reported that in 12

Figure 9
patients pulse labeled with $^{14}$C-cholesterol and treated with CPIB, there was a decreased slope of the decay curve of SA of plasma cholesterol in five patients, no change in five, and a slight increase in two. Since in 10 out of 12 patients the curves failed to show an enhanced rate of decay (i.e., increased slope), they inferred that synthesis was actually depressed. Since, in most of their cases, the increments in fecal excretion of total endogenous steroids exceeded the decrements of plasma cholesterol content, they concluded that the excess sterol excreted came from body stores. The early rise in SA of plasma cholesterol observed by us would support this view. Since Grundy et al.4 found that CPIB caused no change in cholesterol absorption, then the most likely explanation of the flattening of the slope of the SA curve of plasma cholesterol would appear to be decreased synthesis or a continued influx of highly labeled (high SA) cholesterol into the plasma pool, or both.

Our results suggest that in the type II subject CPIB has two independent effects: (1) it appears to inhibit synthesis of cholesterol (as evidenced by the reduction of plasma cholesterol levels and flattening of the plasma SA curve), and (2) it increases the excretion of fecal neutral sterols and bile acids. In the type IV subject our data suggest inhibition of synthesis of cholesterol (reduction in plasma levels and in slope of SA curve of plasma cholesterol), but no effect on the excretion of neutral or acidic sterols.

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Mode of Action of Chlorophenoxyisobutyric Acid on Cholesterol Metabolism in Man

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