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The Mechanism of Action of new Hypocholesterolemic Substances

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Starting from the present knowledge on the importance of Coenzyme A for the synthesis of cholesterol and lipids, it was presumed to be possible to interfere actively with these substances by finding drugs inhibiting the acetylizing activity of Coenzyme A.

Therefore, in connection with the researches carried out by *Cottet* on the hypocholesterolemic effect of phenylethylacetic acid, new molecules were synthesized, in which, the phenylic group was substituted by a "diphenylic", "diphenylilic", "stilbenic" or "diphenylethanic" group (1). Such molecules proved capable of blocking to different degrees the processes of acetylation "in vitro" both of an aromatic amine (2, 3) and of choline (4).

These molecules inhibit "in vitro" the oxygen consumption of liver, heart or brain homogenate; this inhibition, however, becomes more marked when the consumption of oxygen increases after addition of certain metabolites of Krebs's cycle (piruvic acid, α-chetoglutaric acid, citric acid [5]). Also "in vivo" the derivates we studied appear to inhibit the acetylation of sulfanilamide (4).

As far as the metabolism of cholesterol and of lipids is concerned, we were able to demonstrate, by using diphenylilethylacetic acid, that a lowering in the incorporation of radioactive 1-^{14}C-acetate takes place both in lipids and in cholesterol. Instead, the oxydation of acetic acid appears to be influenced to a lesser degree (6, 7). A direct comparison of activity between phenylethylacetic acid and diphenylilethylacetic acid shows that the latter substance is about ten times more active than the former. "In vivo", furthermore, in a test producing increased endogenous synthesis of cholesterol and lipids (hypercholesterolemia and hyperlipemia caused by Triton), diphenylilethylacetic acid exercises a hypocholesterolemic and hypolipemic effect (8, 9). Diphenylilethylacetic acid has also been used in clinic at doses of 300 mg per day in patients

with hypercholesterolemia and hyperlipemia (10, 11), and the results appear to be favourable.

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