interaction with Phe-120, which the model demands, and evidence based on coupling constants that the sugar is in the 2′-*endo* form, which model building has shown to offer small hindrance to rotation around the glycosidic bond. Meadows *et al.* quote unpublished crystallographic data to bear out this interesting observation (and it would be ungenerous to inquire which results came first), and they see this as a novel example of an induced fit in an inhibitor. Some speculations on the enzyme mechanism provoked by these structural studies have been published (Roberts *et al.*, *Proc. US Nat. Acad. Sci.*, **62**, 1151; 1969).

BIOSYNTHESIS

Feedback Control for Bile Salts

from a Correspondent

Do orally administered bile salts exert negative feedback control on bile salt biosynthesis in the mammalian liver? This apparently simple question has received contradictory answers, but some recent work may help to clear up the matter.

Some past discrepancies may stem from the methods used to examine this biosynthetic reaction. In most studies of product inhibition, liver slices are incubated with a radioactive precursor in the presence or absence of the end-product. But, because liver secretes all its bile salt into the bile duct, bile salt synthesis can be examined *in vivo*. Bile is collected from rats with a bile fistula and rates of output (and synthesis) are deduced for each salt; the fistula prevents bile salts from reaching the intestine for recycling to the liver. During the first six to twelve hours after insertion of the fistula the liver pumps out almost all of its bile salts, and then starts to replace them by accelerating their usually rather slow synthesis. To test for a feedback effect, a bile salt (for example, taurocholate) is infused into the intestine at this point to see whether the enhanced synthesis is inhibited.

Duodenal infusion of taurocholate at the calculated normal rate has previously failed to reduce the enhanced synthesis. (The "normal" rate is calculated from absorption efficiency, hepatic pool size and number of enterohepatic circulations of bile salt per day.) But Mosbach's group in New York has recently shown (*J. Lipid Res.*, **10**, 646; 1969) that earlier estimates of absorption efficiency and pool size in the rat were erroneous (too high and too small, respectively) and that infusion of taurocholate at three times the rate previously used reduces the rate of synthesis of bile salts (both taurochenodeoxycholate and taurocholate) to normal.

Others have established without difficulty that duodenal infusion of taurocholate inhibits the hepatic biosynthesis of cholesterol. In principle, this alone might be sufficient to account for the decrease in the production of bile salts (cholesterol being the precursor of all bile salts), but Mosbach suggests that taurocholate may also inhibit the 7α-hydroxylation of cholesterol, the first biosynthetic step between cholesterol and bile salt.

These results apply only to rats. Although there has been a preliminary report of the suppression of bile acid synthesis in some patients by orally administered bile salts (S. M. Grundy *et al.*, *J. Clin. Invest.*, **45**, 1018; 1966), Mosbach's conclusions should not be hastily extrapolated to man. Such an extrapolation was made a few years ago, when the feedback effect of dietary cholesterol on cholesterol biosynthesis, well established in rats, was presumed to be effective in man. This led to much confusion in discussions of the harmful effects of cholesterol in the normal human diet.

HEART ATTACKS

Role of Catecholamines

from our Medical Biochemistry Correspondent

Is there a connexion between concentrations of catecholamines and fatty acids in the blood and the occurrence of heart attacks? Evidence has been conflicting, but some recent results suggest that these substances are important.

Last year Oliver, Kurien and Greenwood found a significant correlation between very high concentrations of free fatty acids in serum and the incidence of irregular heart beats and death after acute myocardial infarction—heart attacks (*Lancet*, i, 710; 1968). Rutenberg *et al.*, however, found no relationship between initial concentrations of free fatty acids in the serum and the development of irregular heart beat, cardiogenic shock and death, but their statistical procedure was not quite the same as that of Oliver *et al.* (*Lancet*, ii, 559; 1969). Rutenberg *et al.* did find, however, that concentrations of free fatty acids tended to increase when complications developed. They concluded that it was the increase in catecholamines rather than fatty acids that brought on the complications.

It is not easy to measure catecholamines in serum, but McDonald *et al.* have recently done this, with interesting results, for fifty men immediately after cardiac infarction and another fifty men of equivalent ages, admitted to hospital for reasons other than cardiovascular troubles. Samples of blood were usually taken within twenty-four hours of admission to hospital and always before the patients had undergone surgery. There was significantly more of the catecholamine noradrenaline in plasma after myocardial infarction than in the other patients (a mean of $0{\cdot}60 \pm 0{\cdot}34$ μg/l. compared with a mean of $0{\cdot}28 \pm 0{\cdot}15$ μg/l.), but there was no difference in the mean concentrations of adrenaline.

In six other patients, undergoing cardiac catheterization, a procedure likely to produce anxiety and so increase catecholamines, the mean concentration of noradrenaline was relatively low (0·21 μg/l.), but the concentration of adrenaline had increased to 0·33 μg/l. Among patients suffering from myocardial infarction, noradrenaline was significantly greater in those with the complication of pulmonary venous congestion ($0{\cdot}68 \pm 0{\cdot}37$ μg/l.) than in those without ($0{\cdot}45 \pm 0{\cdot}26$ μg/l.).

Clearly there does seem to be an increase in plasma catecholamines after myocardial infarction, and there is some evidence that the occurrence of complications is related to very high concentrations of noradrenaline. A healthy heart, however, can survive very high concentrations of noradrenaline with no ill effect. For example, McDonald *et al.* found mean concentrations of 4·4 μg/l. of noradrenaline and 0·99 μg/l. of adrenaline in three racing drivers between two and ten