urinary kallikrein, but to a decreased excretion or production of this enzyme by the kidneys of the hypertensive rats.

Résumé. L'amoindrissement de l'activité kallikréinique urinaire chez les rats hypertendus (technique de GROLLMAN[10]) est due à une diminution de l'élimination de cet enzyme, puisque la cinétique enzymatique, l'action des inhibiteurs sur l'activité estérasique (sur BAEE) et oxytoxique est égale à celle trouvée chez la kallikréine urinaire des rats normaux.

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Effect of Prostaglandin E_1 on Cholesterol Biosynthesis in Rat Liver

In 1952 it was first reported that the ingestion of synthetic diets containing a large proportion of vegetable fat resulted in a reduction in the level of plasma cholesterol[1]. Subsequent studies demonstrated that the isocaloric substitution of an unsaturated fat diet for a saturated fat resulted in a decline of plasma cholesterol concentration[2-3].

The mechanism whereby unsaturated fat feeding lowers plasma cholesterol is far from being clarified. Since the liver is regarded as the major source of circulating cholesterol[4-5], the reduction in plasma cholesterol under these dietary conditions may be due to a decrease in the cholesterogenic acticity of the liver induced either by the polyunsaturated fatty acids or by some of their derivatives. Polyunsaturated fatty acids are precursors of prostaglandins[6]. Several mammalian tissues have been found to be capable of converting polyunsaturated fatty acids into prostaglandins[7-8].

It has also been postulated by KUNZE and VOGT[9] that the rate of prostaglandins formation within a tissue is determined by the availability of the substrate for the PGE synthetase. Several lines of evidence indicate that increased release of prostaglandins in tissues occurs after i.v. administration of polienoic fatty acids[10] and phoshолipase A[11].

Furthermore, in presence of essential fatty acids deficiency, there is a defect in the synthesis of prostaglandins[12]. This close association between polienoic fatty acids and prostaglandins suggested us a possible mechanism of action of essential fatty acids on cholesterol biosynthesis. If it could be demonstrated that prostaglandins have an inhibitory effect on hepatic cholesterogenesis, the decline in plasma cholesterol which follows the ingestion of polyunsaturated diet could be explained in terms of an increase formation of PGE_1 within the liver.

In order to shed some light on this hypothesis we studied the in vitro effect of PGE_1 on cholesterol synthetic activity of rat liver slices.

Materials and methods. Male Wistar rats (200–250 g) were used in this study. Liver slices were incubated in Krebs bicarbonate buffer in presence of ^{14}C-acetate and various amounts of PGE_1 (Upjohn, Company, Kalamazoo, Michigan, 49001). The rate of incorporation of labelled acetate into cholesterol (as digitonin precipitable sterols) fatty acids and metabolic CO_2 were assayed as described in a previous report[13].

Results and discussion. The in vitro effect of PGE_1 on the rate of incorporation of labelled acetate into fatty acids, cholesterol and CO_2 is illustrated in Figure 1. The addition of minute amounts of PGE_1 to the incubation system resulted in a stimulation of both cholesterogenesis and fatty acid synthesis. As the concentration of PGE_1 was increased we observed an inhibition of cholesterol and fatty acids synthesis as well as a significant reduction in the production of radioactive CO_2. PGE_1 therefore appears to have two opposite effects on the incorporation of acetate by liver slices, which is dependent on its concentration in the liver tissue. As both fatty acids and sterol synthesis, as well as CO_2 production, are equally affected by PGE_1, it may be speculated that PGE_1 interferes with the formation of active acetyl, the precursor for the biosynthesis of fatty acids and sterols.

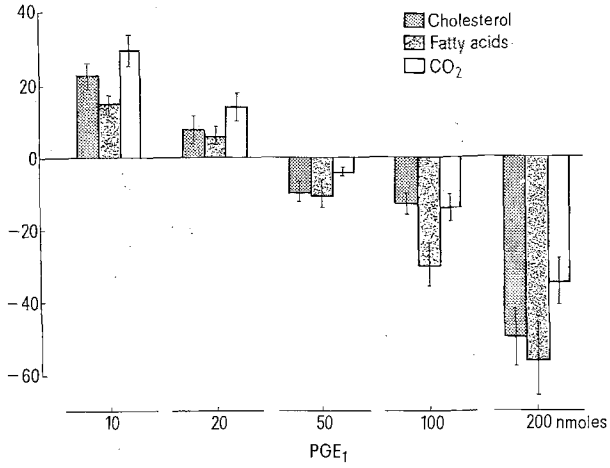

Fig. 1. The effect of increasing amounts of PGE_1 on the incorporation of acetate-2-C^{14} into cholesterol (as digitonin precipitable sterols) fatty acids and metabolic CO_2. Each flask contained liver slices (0.5 mm thick) and 5 ml of Krebs' bicarbonate buffer (pH 7.4), 25 μmoles of sodium acetate -2-C^{14}(specific activity 0.05 μCi/μmole).

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We should not rule out, however, the possibility that PGE_1 produces its effect by changing the acetate pool within the liver cell. If more unlabelled acetate becomes available in the hepatocytes, the rate of synthesis of fatty acid and sterols (as measured by the in vitro incorporation of ^{14}C-acetate) may be underestimated.

It is difficult to predict whether the effect of PGE_1 which we observed in vitro also occurs in vivo, as the amount of PGE_1 used in this study may be far above the concentration of prostaglandins which is present in the liver in normal conditions.

In the majority of tissues, the concentrations of both free and bound prostaglandins are very low; but there is evidence that nutriotional[10] and hormonal[8] stimuli can increase the concentration of PGE_1 by stimulating a rapid rate of de novo synthesis. Furthermore it should be taken into account that probably only a small proportion of PGE_1 present in the incubation system is taken up by the liver, so that the intracellular concentration of PGE_1 may be within physiological levels. It is also important to stress that the concentration of PGE_1 which inhibits in vitro fatty acids and sterol synthesis in the liver is much lower than that which is known to inhibit norepinephrine-induced lipolysis in adipose tissue[14].

The mechanism of action of PGE_1 in the mammalian tissue is still a matter of controversy. However, a great deal of evidence has now been accumulated which indicates that many of the pharmacological effects of PGE_1 are present in those systems where cAMP formation can occur. PGE_1 may act through an inhibition of cAMP accumulation, as in adipose tissue[14–15], or, more frequently through an increase of the intracellular level of cAMP, as has been demonstrated in some tissues, such as thyroid[16] heart[17] and kidney[18].

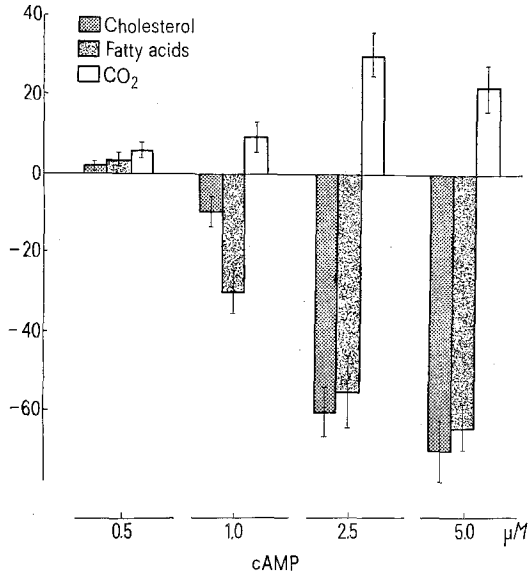

Fig. 2. Effect of increasing amounts of cyclic 3′, 5′-AMP on the incorporation of acetate-2-C^{14} into cholesterol (DPS), fatty acids and metabolic CO_2.

For these reasons we also studied the in vitro effect of cAMP on the synthesis of cholesterol and fatty acids by liver slices. The addition of cAMP to the incubation system was followed by a significant suppression of the rate of incorporation of acetate in both fatty acids and digitonin precipitable sterols. CO_2 production was found to be higher after the addition of cAMP as compared to the controls. These data are in accord with the results recently found by BRICKER and LEVY[19]. These results indicate that PGE_1 and cAMP have a similar effect on hepatic synthesis of fatty acids and sterols, although they may act at different biochemical levels. This close association would suggest that either PGE_1 could exert its effect on hepatic synthesis of lipids through a stimulation of cAMP formation, or that accumulation of cAMP in the liver cells leads to a release of PGE_1 which in turn inhibits lipid synthesis from acetate.

Whichever mechanism is involved, we feel that this observation provides a tool for a further understanding of the role essential fatty acids on lipid metabolism in mammalian liver. It may be reasonable to assume that whenever hepatic concentration of these precursors increases because of a high exogenous intake, the production of prostaglandins may also be increased.

Riassunto. La prostaglandina E_1 (PGE_1) ha un duplice effetto sulla sintesi epatica del colesterolo: a basse concentrazioni determina un incremento della incorporazione di acetato in colesterolo, mentre a concentrazini superiori a 50 nmoli essa determina una riduzione di questo paramentro.

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Mechanism of Drug-Induced Chronic Otic Lesions. Role of Drug Accumulation on the Melanin of the Inner Ear

Although drugs such as salicylic acid may cause a hearing reduction of short duration, most of the injuries to the inner ear are of a chronic and serious nature[1]. They are caused by many compounds, but two main groups can be distinguished: 1. the streptomycin group of antibiotics, and 2. quinine and its many synthetic successors (especially chloroquine). The injuries caused by all these drugs have many characteristics in common. Both hearing and balance difficulties may appear. Functional disturbances correspond to evident histopathologic changes. High dosage and long-term therapy are usually involved. The damage has a marked tendency to be irreversible. Furthermore, symptoms will often appear only after a long latent period – several months after the medication has been discontinued.

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