IMPORTANCE OF THE HEPATO-INTESTINAL CIRCULATION OF BILE SUBSTANCES

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It has long been known that the bile acids, when their role in the intestine is complete, are absorbed in the ileum into the blood of the portal vein, and are then secreted again by the liver in the bile. Recent observations have shown that about 90% of the bile acids entering it are reabsorbed in the intestine. The remaining 10% undergo chemical conversion under the influence of the intestinal microflora, and the greater part is excreted from the organism. Most of the bile acids therefore circulate between the liver and intestine. Because of this the liver synthesizes new bile acids at a very moderate intensity, utilizing only about 10% of its potential capacity for the synthesis of these compounds [11], and only in special conditions (when reabsorption of these acids is disturbed) is its whole capacity used. Bilirubin also participates in this circulation between the liver and intestine, although it is reabsorbed to a relatively much smaller degree and is more abundantly excreted from the organism. These processes are a special example of a more widespread phenomenon—the circulation of substances between the blood and alimentary tract, a phenomenon to which great importance is currently attached as the link between digestion and certain general metabolic processes [3, 7, 8].

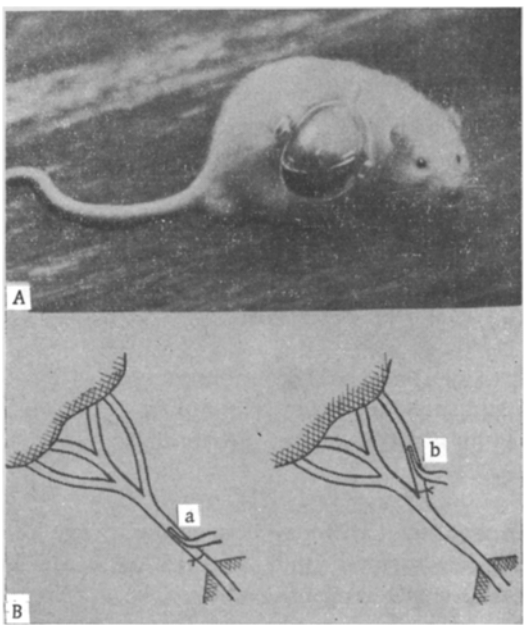

Fig. 1. Cannulation of common and lobar bile ducts. A—rat after operation with bile receiver; B—scheme of operations.

These facts suggest that the hepato-intestinal circulation of bile substances is of great importance to the external secretory activity of the liver. However, the role of this circulation in individual processes has received very little study, and the results of its disturbance have been inadequately explained, because no methods are available for investigating bile formation when this circulation is present or when it is disturbed.

Methods have been developed to carry out such investigations in the authors' laboratory. L. S. Vasilevskaya [1] modified the technique of cannulation of the common bile duct in rats, suggested a modified bile receiver, and developed a new method of cannulation of the lobar bile duct. In the first case the animals lose all their bile and no circulation of bile takes place, whereas in the second they lose only part of the bile and the rest continues to circulate between the liver and intestine (Fig. 1).

By using these methods, attempts were made to study the role of the hepato-intestinal circulation of bile substances in adaptation of the liver to qualitative changes in the diet. To assess the external secretory activity of the liver in

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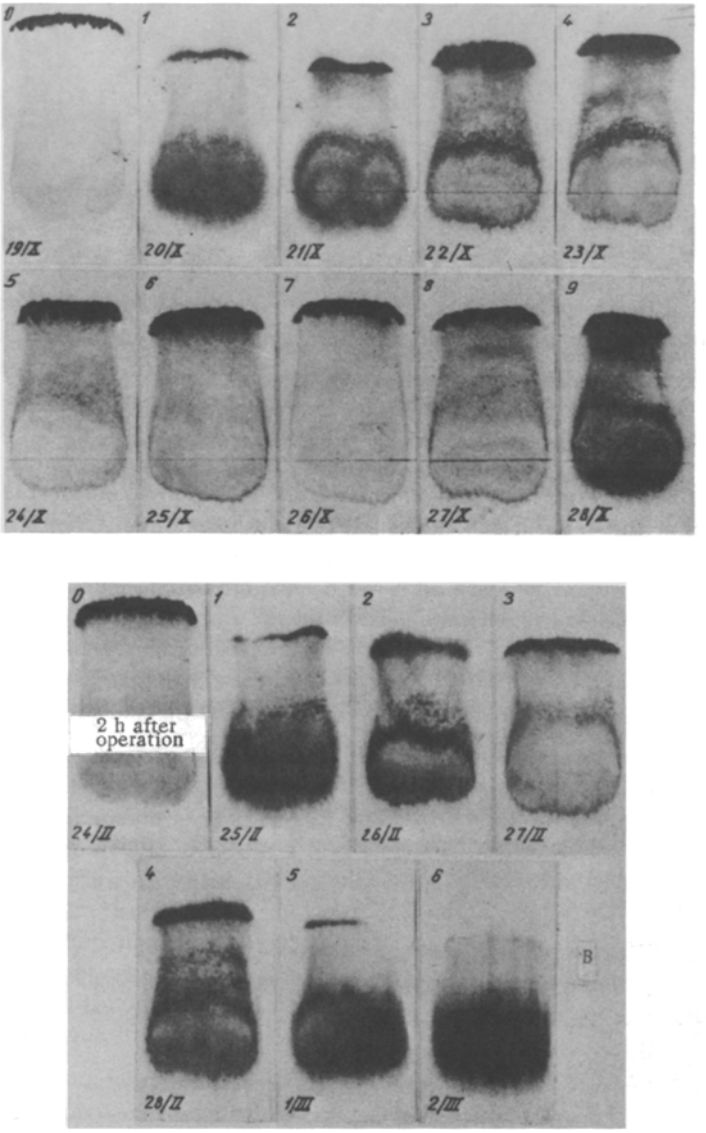

Fig. 2. Lipid complex in rat bile. A—on a normal diet and on different days after cannulation of the common bile duct (concentration of complex restored on 3rd-4th day after operation); B—on a deficient diet (formation of complex grossly disturbed after operation).

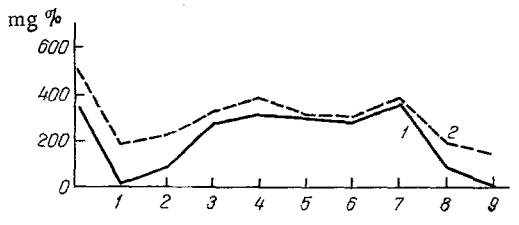

Fig. 3. Correlation between content (in mg%) of lipid complex and cholic acid in bile. 1) Lipid complex of bile; 2) cholic acid. Abscissa—days of experiment.

these investigations, observations were kept on secretion of the lipid complex and of its main components in the bile.

According to recent findings, most organic substances of the bile are present as a single complex, which can be called the lipid complex (formally the lipoprotein complex). In its composition, this complex includes bile acids, phospholipids, cholesterol, bilirubin, and often a small amount of protein. Initially a complex of this type was discovered in bile in the human gall bladder [13, 14, 17] and it was regarded as a product formed actually in the gall bladder. The work of M. F. Nesterin, R. V. Narodetskaya,

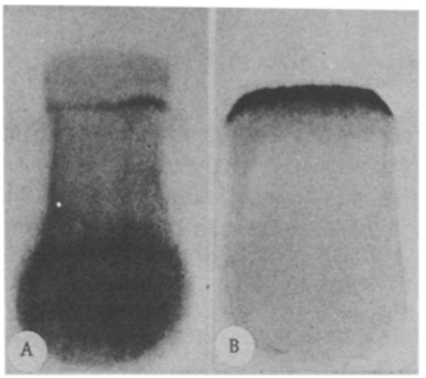

Fig. 4. Effect of addition of cholic acid to bile in vitro on content of lipid complex. Bile obtained from animals on a deficient diet: A—before addition; B—after addition of cholic acid. Content of complex restored and additional lipid fractions disappeared.

and G. K. Shlygin [5, 6], undertaken on dogs, showed that this complex is formed actually in the liver tissue. The presence of this complex was demonstrated in the bile of different animals, including those without a gall bladder, such as rats [1]. This complex is constantly secreted in human C bile [4].

No such complex is present in the other digestive secretions, and in particular, none is found in pancreatic or intestinal juice [5]. This compound in thus specific for bile.

The lipid complex of the bile is evidently micellar in nature. It is a transportable chemical substance with a structure enabling large quantities of phospholipids—which are insoluble in water—to be separated and transported as a homogeneous solution in the composition of the bile. In the intestine, this complex apparently plays an important role in digestion and absorption of lipids. On electrophoresis on paper, the lipid complex shows extremely high mobility, higher than that of the globulins and albumins of the bile. When stained with Sudan black, it gives a characteristic serrated pattern.

Observation of secretion of the bile lipid complex has widened opportunities of assessing the liver function, for it reflects the ability of the liver to secrete a large quantity of different components and to unite them into a single entity.

This index was therefore mainly used in the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on Wistar rats in which the common and lobar bile ducts were cannulated [1]. These methods make it possible to investigate bile formation both in the presence and in the absence of hepato-intestinal circulation. During the investigation the animals were kept on special experimental diets—low-protein and hypolipotropic [9], and also on a balanced control diet. The lipid complex in the bile was determined by electrophoresis on paper [6], the cholic acid [15] and bilirubin [10] were determined as described elsewhere, phospholipids by means of extraction with methanol and chloroform [12], and total phosphorus by Zamychkina's method [2].

EXPERIMENTAL RESULTS AND DISCUSSION

Experiments to discover the role of the hepato-intestinal circulation were first carried out on animals receiving a normal balanced diet.

After cannulation of the common bile duct and, consequently, disturbance of the circulation of bile substances, the following changes were observed in the rats on a balanced diet (Fig. 2, A). By the end of the 1st day and on the 2nd day the secretion of bile lipid complex was reduced, but by the 3rd-4th day it had recovered and remained at almost the normal level until the end of the experiment (9-11 days). After cannulation of the lobar bile duct, the same changes in principle were observed, but the concentration of complex fell much less initially, and subsequently recovered more rapidly and more completely.

However, the differences were particularly marked in the experiments on animals with a deficient diet. For instance, in animals receiving a low-protein (6% protein) and, in particular, a hypolipotropic diet, i.e., a diet deficient in choline and methionine, with amino-acid inbalance, and with cannulation of the common bile duct the secretion of bile lipid complex was sharply depressed (Fig. 2, B). The fraction contained in this complex was clearly visible only during the first hours (when the circulation was still in progress), and subsequently it became indistinct. This means that secretion of the complex, when disturbed as a result of interruption of the circulation, cannot be adequately restored on a deficient diet. The concentration of complex in the bile fell sharply, and this was accompanied by qualitative changes also:

the band of the complex was indistinct, its characteristic pattern was obliterated, and additional lipid fractions – evidently protein-lipid compounds not normally present – appeared in the bile.

The results of investigation of the content of individual components of the complex showed that in this case the secretion of bile acids was most disturbed, and their synthesis was inadequate for binding the various components of the bile into a single complex. The clear (statistically significant) correlation between the concentration of complex and of cholic acid in the bile was in agreement with this conclusion (Fig. 3). Further confirmation was obtained by experiments in vitro. Addition of cholic acid to the bile obtained in these conditions led to an increase in concentration of the lipid complex and, at the same time, to disappearance of the additional lipid fractions (Fig. 4).

These changes under the influence of a deficient diet could be observed in the absence of hepato-intestinal circulation of bile substances.

Completely different results were obtained when this circulation was intact (in animals with cannulation of the lobar bile duct). In animals on a hypolipotropic diet, only slight changes were observed, mainly expressed by a decrease in the amount of complex secreted during the 24 h, and in a less distinct pattern on electrophoresis. Its concentration remained fairly high. In animals receiving a low-protein diet, no significant changes took place for 20-30 days or more. Secretion of the lipid complex remained in a satisfactory state throughout. The animals lived much longer than those in which the common bile duct was cannulated.

Hence, the hepato-intestinal circulation of bile substances in these conditions plays an adaptive role, preventing for a considerable time any adverse effect of the deficient diet on the external secretory function of the liver. It was stated above that because of this circulation the liver synthesizes only part of the essential bile acids, the rest returning to the liver ready made and being reexcreted by the liver in the bile. The concentration of active components in the bile necessary for digestive processes is created with a smaller functional load on the liver.

Clearly the hepato-intestinal circulation facilitates metabolism and results in economy in synthetic work by the liver. It thus plays a very important role in the external secretion of the liver.

In normal conditions, the quantitative and qualitative variations in the composition of the diet are not reflected in the secretory function of the liver because of its great reserve capacity and because of the hepato-intestinal circulation of bile substances. However, if this circulation is disturbed, the character of the diet begins to have a very considerable effect: a deficiency of protein or of lipotropic substances in the diet is quickly and considerably reflected in formation of the principal bile components, especially the lipid complex and bile acids.

The state of the hepato-intestinal circulation of bile substances must be taken into consideration in clinical practice. In many pathological conditions – diseases of the intestine with changes in absorption processes in the ileum, diseases of the gall bladder and of the liver itself – the circulation may be disturbed to some degree. States may develop similar to those described experimentally, marked by disturbance of bile formation and, above all, by deficient synthesis of bile acids.

In these cases restoration of the circulation and stimulation of bile acid synthesis by special therapeutic diets are particularly important.

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