NUTRITIONAL REGULATION OF PANCREATIC AND BILIARY SECRETIONS

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INTRODUCTION

Pancreatic exocrine secretion of a wide spectrum of enzymes together with biliary secretion which is rich in bile acids, phospholipids and cholesterol represent major digestive secretions and allow enzymic degradation of many dietary components in mammals. In animals, experimental diversion of these secretions out of the gastrointestinal tract leads to decreased digestive utilization of the diet. In humans, various pathological states lead to severe malnutrition by reduction of the gastrointestinal digestive capacity (DiMagno *et al.* 1973). Under physiological conditions it is now well known that the quantity of pancreatic enzymes secreted is sufficient for digestion of approximately ten times the amount of food usually ingested (Corring, 1980). However, digestive capacity may be dramatically modified

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by numerous stimuli and among them is food. Very diverse dietary factors may alter digestive secretions: carbohydrates, proteins, lipids, trace element deficiencies, enzyme inhibitors, dietary fibre, physical state of the diet,...,etc.

Because it is not possible to summarize all these effects in the present review, we have concentrated on the adaptation of pancreatic and bile secretions to the diet. Moreover, because of its specific action on intraluminal bile acids and on their metabolism, the specific effect of fibre on bile secretion is discussed. In all cases, attention has been focused on the mechanisms involved in the relationship between digestive secretions and food.

PANCREATIC SECRETION AND DIETARY CHANGES

ADAPTATION TO THE DIET

Pavlov (1879) observed that the pancreas is able to modify its secretion in response to the composition of diet. This phenomenon has been widely confirmed since then, using more and more sophisticated techniques (Desnuelle *et al.* 1962; Corring, 1980). In animals proteolytic enzyme activity, either in pancreatic tissue or in pancreatic juice entering the duodenum, is modified by the protein content of the diet, while amylase and lipase (*EC* 3.1.1.3) activities are respectively dependent on the carbohydrate and lipid contents in the diet. These variations depend on parallel increases or decreases in enzyme biosynthesis (Reboud *et al.* 1966; Poort & Poort, 1980). In humans, too few studies have been performed so far to demonstrate clearly the adaptation of pancreatic secretion to diet composition. According to Lebenthal *et al.* (1981) it does exist in premature infants, but Emde *et al.* (1985) failed to demonstrate any adaptive change in pancreatic amylase and lipase secretion in response to a 10 d continuous intraduodenal infusion of a high-carbohydrate, low-fat diet in adults.

During the past 20 years, studies of pancreatic adaptation to the diet have covered such enzymes as phospholipase (Prost *et al.* 1978) and carboxypeptidases (Berger & Schneeman, 1986). Regarding adaptation of colipase, published results are contradictory. In rats Girard-Globa & Simond-Cote (1977) reported adaptation of colipase to dietary lipids, whereas Vandermeers-Piret *et al.* (1977) did not observe any in either rats or mice. These conflicting findings may be explained by quantitative and qualitative differences in dietary protein ingestion (Saraux *et al.* 1982). Colipase adaptation to the amount of dietary lipids has been demonstrated in pigs fed on isonitrogenous diets (Mourot & Corring, 1979).

The idea that there are minimal and maximal limits to secretion appears in the case of lipase activities in response to increasing amounts of dietary lipid. Sabb *et al.* (1986) demonstrated that lipase activity is not stimulated when dietary fat energy supply represents 196 kJ (47 kcal) or less of the total dietary energy intake; beyond this point, lipase activity increases and is maximally stimulated when fat represents 225–280 kJ (54–67 kcal) of the total dietary energy intake. In the same way, Bucko & Kopec (1979) reported that the maximal pancreatic response to maize oil adaptation is obtained with a 180 g maize oil/kg-enriched diet. Similar observations were reported by others (Gidez, 1973; Saraux *et al.* 1982). In this connexion, pancreatic lipase activity appears to be influenced by the type of fat ingested (Deschodt-Lanckman *et al.* 1971; Saraux *et al.* 1982; Simoes Nunes, 1986). According to Sabb *et al.* (1986), pancreatic lipase adapts primarily to the amount of dietary fat and is affected by the type of the fat only below the level of maximal enzyme response.

Such limits in adaptation of other pancreatic enzymes have not been reported. Amylase is enhanced by increasing the ingested amount of starch (Noirot *et al.* 1981). Pancreatic proteolytic enzyme secretion is proportional or shows a 'purposive' adaptive response to the quantity of nitrogen intestinally infused in man (Vidon *et al.* 1978), or orally ingested

in the rat (Schick *et al.* 1984*b*). It is also sensitive to the type of protein orally ingested in pigs (P. Valette & T. Corring, unpublished results), or intraduodenally infused in rats (Berger & Schneeman, 1986).

It has been found by several authors that pancreatic adaptation to a dietary change is completed within 5–7 d and a new steady-state is established (for example, Corring & Saucier, 1972; Bozkurt & Haberich, 1985). Interestingly, long-term (6–9 months) dietary changes produce pancreatic exocrine responses similar to those reported in short-term studies in rats (Houghton *et al.* 1983). According to Poort & Poort (1980), biosynthesis of pancreatic enzymes is modified 5 d after feeding rats with a protein-rich diet *v.* a carbohydrate-rich diet. Other authors showed that pancreatic biosynthesis in reponse to dietary changes occurred even earlier. For instance, Dagorn & Lahaie (1981) reported that changes in synthesis rate occurs as early as 24 h after alteration in dietary composition, thus preceding changes in tissue levels of enzyme. In the pig, amylase activity in the pancreatic juice is augmented throughout the first 2 h following increased starch intake (Simoes Nunes & Corring, 1979). In trying to explain why enzyme adaptation takes a relatively long time to stabilize after a change of diet, it is suggested that it depends on the adjustment to the new diet of other digestive processes such as gastric emptying or intestinal motility (Corring, 1977). On the first experimental day, changing the amount of substrate ingested would represent a stimulus which must be repeated (intake of several meals of the new diet) in order to get a full change in the bulk of gastrointestinal tract content. Indeed, Bozkurt & Haberich (1985) found a close relationship between the time interval required for adaptation and the extent of change in dietary components in rats: the adaptation of proteolytic enzymes requires about 7–8 d when the dietary protein content varies from 100 to 570 g/kg and only 3–4 d when varying from 240 to 570 g/kg. In addition, it has been emphasized that adaptation to a protein-rich diet occurs at a faster rate than adaptation to a carbohydrate-rich diet (Lahaie & Dagorn, 1981) and lipase activity reaches its maximum even faster (Deschodt-Lanckman *et al.* 1971), suggesting that different mechanisms are involved in adaptation to each type of dietary nutrient.

Today, pancreatic adaptation to diet appears much more complex than was expected by the first experimenters. Each enzyme behaves differently, depending on the amount and the type of substrate ingested. The mechanisms involved are still largely unknown and we will now consider some hypotheses for explaining adaptive processes.

MECHANISMS OF PANCREATIC ADAPTATION

In an animal adapted to a specific nutrient-enriched diet, the high level of this nutrient in the digestive tract is very rapidly followed by increased corresponding enzyme levels in the pancreas, although no contact between the nutrient and the pancreas has occurred. The ingested nutrients very rapidly undergo physical and biochemical degradation, initially in the stomach. The stomach evacuates a mixture of nutrients and hydrolysis products into the duodenum. Therefore, the information sent to the pancreas may be generated by the substrate or its hydrolysis products. Several studies are described later which attempt to identify which product was responsible for pancreatic adaptation to diet and which second messenger was involved.

The increase induced by starch on amylase synthesis is comparable to that induced by its hydrolysis products, glucose (Robberecht *et al.* 1971) or D-glucose (Grossman *et al.* 1944). Nevertheless, according to Noirot *et al.* (1981) starch feeding is a better amylase stimulant than simple sugar feeding. Replacement of intact protein by its acid- or enzymic hydrolysis products in the diet does not lead to any increase in proteolytic enzyme levels but, on the contrary, to their decrease (Grossman *et al.* 1944; Howard & Yudkin, 1963), suggesting that the intact molecule is responsible for pancreatic adaptation to a protein-

enriched diet. However, these studies were performed in the rat, which is unusual because only specific intact proteins significantly modify pancreatic secretion (Schneeman *et al.* 1977; Green & Miyasaka, 1983). Similar studies using oral ingestion of hydrolysis products have not been performed yet in other species. However, in man and in the dog pancreatic secretion is stimulated by peptides and intestinal infusion of amino acids (Meyer & Kelly, 1976; Meyer *et al.* 1976) as well as by intestinal infusion of lipids and their hydrolysis products (Malagelada *et al.* 1976). It is now assumed that hydrolysis products act on the intestinal mucosa which secretes the so-called second messenger. This hypothesis is clearly sustained by the following findings. First, intravenous fat and amino acids do not affect pancreatic secretion in dogs (Stabile *et al.* 1984; Burns & Stein, 1987), while in humans intravenous lipid does not stimulate pancreatic secretion (Edelman & Valenzuela, 1983). Parenteral administration of glucose has been shown either to have no effect on amylase secretion in the dog (Stabile *et al.* 1984) or to decrease it (dog, Saito *et al.* 1978; humans, Dudrick *et al.* 1970; pig, Simoes Nunes & Corring, 1981). Only Konturek *et al.* (1979) found a significant increase in pancreatic enzyme secretion during short-term intravenous administration of lipid and amino acid infusions in dogs suggesting that these molecules have to pass through the intestinal wall to provoke the pancreatic response to food ingestion. Nevertheless, such results are inconsistent with those of most authors.

It is of note that almost all the experimental findings emphasize the effect of hydrolysis products on the pancreatic secretion before their intestinal absorption, indicating an active involvement of the intestinal mucosa through the release of the second messenger. Thus, Dick & Felber (1975) have reported that injection of duodenal extracts from rats fed on different meals into the coeliac artery of recipient rats elicits the secretion of related pancreatic enzymes. Simoes Nunes & Corring (1980) reported very similar results in the pig and Simoes Nunes (1982) showed in addition that pancreatic adaptation to dietary carbohydrates and lipids is no longer observed after proximal small intestine bypass in the pig. In contrast and according to Simoes Nunes (personal communication) pancreatic proteolytic enzyme adaptation to dietary proteins does not depend on the proximal small intestine. Bozkurt & Haberich (1985) reported that starch instillation into the duodenum leads to a rapid increase in amylase secretion, whereas intraduodenal amino acids and lipids somewhat delay the respective responses of proteolytic enzymes and lipase. If, as seems likely, the intestinal mucosa is involved in the adaptation of the pancreas to the diet, the mechanisms are probably different for each enzyme considered (Bozkurt & Haberich, 1985) and would involve mainly peptides. Information concerning nervous control of the pancreatic adaptation to the diet is scarce. According to Morisset & Dunnigan (1967) pancreatic adaptation to the diet is not affected in the vagotomized rat.

Among regulatory peptides, cholecystokinin is often considered to be the main intestinal factor for pancreatic adaptation to diet. According to Green *et al.* (1986), cholecystokinin is involved in the pancreatic protease adaptation to dietary protein in the rat. It is known that cholecystokinin is released in the intestine by food substances and their hydrolysis products. In the rat, intact dietary proteins, but not casein hydrolysate, are potent stimuli of cholecystokinin (Liddle *et al.* 1985), as are fat and carbohydrate, although to a lesser extent than casein (Douglas *et al.* 1988). In man, according to Hopman *et al.* (1985), fat and protein, but not starch, are effective stimuli for the secretion of cholecystokinin, when ingested in equal amounts. However, according to Bozkurt & Haberich (1985), the peptide does not have any specific effect on proteolytic enzymes, but rather a general stimulatory action on every pancreatic enzyme. In the pig, Corring & Chayvialle (1987) reported that cholecystokinin, as well as secretin, somatostatin and pancreatic polypeptide, are not involved in the respective adaptation of amylase and lipase to dietary carbohydrates and lipids. According to Wood *et al.* (1988), neurotensin does not control lipase adaptation to

dietary lipids in the rat. If peptides, which are known to regulate the exocrine pancreas, do not play an essential role in the adaptation of secretion to the diet, the involvement of currently unknown peptide-like components is suggested (Dick & Felber, 1975; Corring, 1977).

Until recently, scientists interested in the problem of how the pancreatic enzymes adapt to the diet have used classical tools such as biochemistry and physiology. However, recent developments in molecular biology are now being used to elucidate the cellular and molecular basis of pancreatic adaptive response to dietary changes.

MOLECULAR REGULATION OF PANCREATIC ADAPTATION

The mechanisms of gene expression have been widely studied during the past 20 years. Among numerous reviews, those of Puigserver *et al.* (1985), Scheele (1986), Goodridge (1987) and Kern *et al.* (1987) have emphasized current knowledge of gene expression and its regulation in the gastrointestinal tract.

Briefly, proteins are synthesized through translation of a pattern provided by mRNA nucleotide sequences. A specific gene sequence located on DNA serves as a template for transcription. The resultant primary RNA transcript is processed through splicing, capping and tailing into mature mRNA. Several factors may influence the rate of gene transcription and mRNA translation: efficiency of transcription, processing and transport of the primary transcript, stability of mature cytoplasmic mRNA and efficiency of translation. Numerous molecular biology techniques are now available to reveal these physiological phenomena (for review, see Goodridge, 1987).

Dietary changes and molecular adaptation

In studies showing pancreatic enzyme adaptation in the rat, protein biosynthesis was directly measured (1) in vivo by single labelling (Reboud *et al.* 1966; Dagorn & Lahaie, 1981; Lahaie & Dagorn, 1981), (2) in vitro by single labelling in pancreatic slices (Reboud *et al.* 1966), or in pancreatic lobules (Wicker *et al.* 1983, 1984; Schick *et al.* 1984*a*, *b*), (3) in vitro by double labelling of pancreatic slices (Poort & Poort, 1980, 1981) followed by separation of radiolabelled protein products by polyacrylamide gel (Poort & Poort, 1981) and isoelectrofocusing (Dagorn & Lahaie, 1981). The first method leads to very rough values because they are expressed relative to total enzyme activity; therefore, secreted proteins are not included. The second method is more precise because it avoids estimation of enzyme activity, but these values express relative differences between one diet and another. Lobules are usually considered to be better models than slices because less tissue is spoilt during preparation, the pieces are smaller and, therefore, better exposed to the incubation medium, while preserving intercellular communications.

In the rat pancreas, twenty-one individual exocrine proteins have been identified by two-dimensional electrophoresis: four forms of procarboxypeptidase, three forms of trypsinogen, two or three forms of amylase, two forms each of chymotrypsinogen and proelastase, one form each of lipase and RNAse (*EC* 3.1.27.5), and four unidentified glycoproteins (Poort & Poort, 1981; Schick *et al.* 1984*a*). In the rat, it has been demonstrated that, following treatment (5 d–3 weeks) with diets containing normal (220 g/kg)–high (820 g/kg) protein levels at the expense of carbohydrate, amylase and the majority of proteases are synthesized in direct proportion to amounts of their corresponding nutritional substrates in the diet. However, chymotrypsinogen, anionic trypsinogen, proelastase 1 and procarboxypeptidases are the most markedly modified. Trypsinogen 3, proelastase 2, RNAase and lipase are not altered (Poort & Poort, 1980, 1981; Schick *et al.* 1984*b*). These findings indicate differential effects of diet on the biosynthesis of serine

proteases and other proteolytic enzymes from the point of view of both extent and timing of enzyme response. Further work is needed to determine whether such effects are modulated by the quality of protein ingested. It appears that study of the regulation of gene expression at the molecular level is necessary for a better understanding of pancreatic adaptation to diet.

Quantification of specific mRNA expression would indicate whether the control of gene expression is located at the translational or pretranslational level. mRNA enzyme concentrations have been measured either by in vitro translation in a cell-free system (Giorgi *et al.* 1984; Wicker *et al.* 1984) or by hybridization of mRNA immobilized on filters to labelled cDNA-cloned probes (Giorgi *et al.* 1984, 1985). A good correlation was observed between values obtained by both methods; the latter tends to be widely used because it is less time-consuming and more sensitive.

In general, the concentrations of all mRNA tested in the previously described studies have been found to vary in the same manner as the intrapancreatic levels of the enzymes. However, the concentration of mRNA coding for amylase is 9-fold higher in a diet with 750 g carbohydrate/kg than in one containing 110 g carbohydrate/kg, whereas the rate of enzyme synthesis is only increased 4-fold (Giorgi *et al.* 1984), suggesting that part of the mRNA may be stored in the cell for a further increase in protein biosynthesis, and that translation of amylase mRNA is a rate-limiting reaction in that case. Concerning serine proteases, elastase (*EC* 3.4.21.36) expression is only significantly increased by a 700 g protein/kg diet, while chymotrypsinogen and especially trypsinogen expression are already increased after a 250 g protein/kg diet (Giorgi *et al.* 1985), suggesting that the control is mostly pretranslational and showing that the expression of genes is not affected to the same extent and with the same sensitivity.

Part of these findings is supported by Wicker *et al.* (1984) who found a good correlation between the protein biosynthesis rate and mRNA levels of amylase and serine proteases (chymotrypsinogen, trypsinogen and proelastase) in rats given high- or low-protein diets and concluded that the control was mostly pretranslational. Moreover, studies using actinomycin D, an inhibitor of transcription, have demonstrated that only trypsinogen 1 and proelastase 1 mRNA half-lives are modified after feeding a protein-rich diet (Puigserver *et al.* 1985).

In conclusion, the control of enzyme synthesis adaptation to a protein-rich diet is probably both pretranslational (transcription or mRNA stability, or both) and translational. Furthermore, the nature and intensity of this control may vary with each enzyme.

As far as control of lipase synthesis is concerned, the first detailed studies have only been published very recently. In a preliminary study it was shown that, on a lipid-rich diet, lipase mRNA increases with pancreatic lipase content, although this increase is more modest than that of proteases after a protein rich diet (Giorgi *et al.* 1983). Administration of a high-lipid, low-carbohydrate diet to rats for 10 d results in an increase in lipase protein synthesis and mRNA contents and a decrease in amylase protein synthesis and mRNA contents (Wicker & Puigserver, 1987; Wicker *et al.* 1988). Ingestion of diets containing 30–200 g fat/kg progressively increases the synthesis of lipase, chymotrypsinogen 1, proelastase 1, whereas no further increase is observed with 250 or 300 g fat/kg in the diet. But procarboxypeptidases and, to a lesser extent, trypsinogen 1 are only increased after consumption of diets containing 250 or 300 g fat/kg. The enhancement of mRNA levels is proportionally less than that of biosynthesis, suggesting a major pretranslational control (via mRNA transcription, process, transport or stability) and a minor translational control. It is of interest to point out that here again there were differences among serine proteases.

It appears, therefore, that different responses can be observed in terms of biosynthesis of

different enzymes hydrolysing the same nutrient. This can be explained partly by the (largely putative) specificity of enzymes towards a particular type of dietary protein. Studies of the variations of gene expression in response to quantitatively identical but qualitatively different protein-enriched diets are needed.

Peptides and molecular adaptation

Several peptides are thought to be intermediates between ingested nutrients and the pancreas. Comparison of the molecular effects of these peptides on pancreatic enzyme synthesis may help to determine their importance in adaptation to diets.

Stimulation with caerulein, a synthetic analogue of cholecystokinin, revealed both coordinate and anticoordinate rate changes (latency, kinetics and extent) in protein synthesis. Acute caerulein (25 μg/kg per h) administered to rats decreases amylase and increases anionic trypsinogens 1 and 2, chymotrypsinogens, procarboxypeptidases and RNAse within 3 h, while cationic trypsinogen 3, elastase 2 and lipase synthesis are not modified (Schick *et al.* 1984*a*). These findings are compatible with those observed after protein-rich diets. However, pronounced changes in individual enzyme biosynthesis are not accompanied by changes in mRNA levels, at least during the initial 6 h of caerulein stimulation (0·25 μg/kg per h); mRNA levels are progressively modified thereafter up to 24 h (Wicker *et al.* 1985). Consequently, it has been suggested that during the early periods of caerulein stimulation, the anticoordinate changes observed in protein synthesis occur at the level of efficiency of mRNA translation. However, additional control at a transcriptional or post-transcriptional level may well take place, particularly with continuation of caerulein administration for 12–24 h. Indeed, Renaud *et al.* (1986) have shown that chronic stimulation of pancreatic secretion with caerulein or cholecystokinin (6 μg/kg and 120 U/kg respectively, twice daily for 7 d) leads to a preferential accumulation of trypsinogen 1 and chymotrypsinogen B mRNA compared with amylase mRNA. This increase is parallel and proportional to protein synthesis, suggesting a pretranslational control. Thus, following caerulein stimulation, there appears to be at least two distinct and overlapping phases in the regulation of gene expression. The anticoordinate changes observed in protein synthesis in both phases are similar, but the initial period may be mostly regulated at the translational level, while throughout the treatment pretranslational regulation takes place and is maintained up to 7 d. Further research is needed to determine whether changes in mRNA levels during late periods of acute treatment or after chronic treatment for several days are mediated by changes in transcription rate, mRNA turnover or both.

The previously discussed findings do not clearly demonstrate that cholecystokinin is the effector of adaptation to a protein-rich diet in the rat. However, variations in enzymic changes described in both diet adaptation and peptide treatment may come from the relatively high doses of peptide administered and the duration of treatment. Therefore, additional experiments with endogenous modifications of cholecystokinin levels (such as trypsin-inhibitor feeding) and exogenous administration of low levels of this peptide are necessary. No doubt the recently improved models for exocrine acinar cell culture will help solve this problem.

As far as adaptation to a high-carbohydrate diet is concerned, insulin may be revealed as a good hormone candidate. To date, it has been demonstrated by hybridization techniques that amylase mRNA levels increase while chymotrypsin and elastase mRNA levels decrease following insulin treatment in rats (Korc *et al.* 1981). These findings suggest that insulin acts at the pretranslational level (transcription or process), as does a high-carbohydrate diet, thus corroborating the hypothesis of a role for insulin in this phenomenon.

Analyses of molecular pathways for the control of transcription and translation are in

progress. Identification of *cis*-acting elements (i.e. sequences in the same DNA molecule as the gene) which may influence the rate of transcription of a specific enzyme in the pancreas was initiated by the Rutter group (Stratowa & Rutter, 1986). Their work has focused on the effect of calcium on the regulation of gene expression in a rat exocrine pancreas cell line AR-42J. They demonstrated that Ca is the main intracellular messenger for trypsinogen induction and for amylase, chymotrypsinogen and procarboxypeptidase inhibition, via the calmodulin route rather than the protein kinase C route. They have suggested that sequences in the 5′ region of these genes contain putative promoter sequences which may interact with the intracellular messenger to influence the transcription rate of a specific gene.

So far, Pinsky *et al.* (1985) have identified the 5′ non-coding region of anionic trypsinogen (1 and 2) mRNA which may influence its rate of translation during caerulein stimulation. The 5′ non-translated regions of dog and rat anionic trypsinogen mRNA have a conserved sequence involving nine contiguous and identical nucleotides; this was not observed in the twenty-nine nucleotides of the 5′ non-translated region of cationic trypsinogen 3. It was suggested that base pairing of this conserved sequence to the 3′ end of the small ribosomal unit may increase the efficiency of mRNA translation by modifying the configuration of the molecule (Kern *et al.* 1987).

Although these findings need refinement, it is of interest to point out that it is now possible to investigate the intracellular pathways of enzyme synthesis control.

BILIARY SECRETION AND DIETARY FAT

BILE RESPONSE TO DIETARY FAT

There has been great interest in the effect of dietary fat on biliary secretion, because the latter represents the main route of cholesterol elimination. Interpretation of experimental results, however, is often complicated by imprecise dietary information, an uncontrolled rate of feeding, or interruption of the enterohepatic circulation. Therefore, it is not surprising that great controversies still persist in this field. In the following account, an attempt will be made to draw general conclusions where the information allows, and to state the remaining problems. The influence of both the quantity and the nature of dietary triglyceride on biliary physiology will be discussed. The role of dietary cholesterol, phytosterols, or bile salts on biliary physiology will not be reviewed here because it has already been discussed (Sarles *et al.* 1970) in connexion with the aetiology of biliary cholesterol gallstones.

Bile salts

Most authors have reported an increased biliary output rate following a raised dietary fat intake (Dowling *et al.* 1971; Redinger *et al.* 1973). However, there are two reports of unchanged (Portman & Mann, 1955; Boquillon & Clément, 1979) and one report of decreased (Davis *et al.* 1977) bile salt secretion rate when feeding rats with increasing quantities of fat. A general conclusion, however, reconciles the results of all the previously mentioned authors, when considering the absolute rate of lipid consumption: secretion of bile salts is definitely stimulated by fat supplementation of a diet initially low in lipid or lipid-free; the secretion rate of bile salts remains unchanged when fat supplementation is superimposed on a diet whose lipid content increases from 70–100 g/kg to 150–200 g/kg. This is confirmed by our own experiment in pigs fed with different lipid-containing semi-synthetic diets (Juste *et al.* 1983). However, the reason why the secretion rate of bile salts does not increase further remains unclear. The bile acid precursor cholesterol would not be the rate-limiting factor since its excretion in bile continues to increase (Juste *et al.* 1983); nor has the secretion rate of bile salts reached a physiological limit, since considerably

higher output rates have been observed on a standard low-lipid diet (Juste *et al.* 1979). A plausible explanation appears to be that there is a limitation in bile acid absorption rate when high concentrations of dietary lipids are present in the intestinal lumen (Fondacaro, 1983).

In the rat, a high-fat diet produced higher levels of glycoconjugated and secondary bile salts compared to a standard diet (Lafont *et al.* 1985). However, this was not observed in the pig (C. Juste, unpublished results) in which the initial level of glycoconjugated bile salts is already very high and the initial proportion of secondary bile salts somewhat higher than in the rat.

Generally speaking, the degree of saturation of dietary long-chain triglycerides does not affect the rate of biliary bile salt output (Redinger *et al.* 1973; Boquillon & Clément, 1979; Juste *et al.* 1986; Jadidi *et al.* 1988). In a number of studies, however, it was shown to be considerably increased following dietary supplements of polyunsaturated fat compared with saturated or monounsaturated fat (Dowling *et al.* 1971; McGovern & Quackenbush, 1973; Ramesha *et al.* 1980). Dietary medium-chain triglycerides are responsible for particularly low secretion of bile salts (Redinger *et al.* 1973; Ladas *et al.* 1984).

Biliary phospholipids

Very few studies have dealt with biliary phospholipid output in relation to dietary fat content. In rats fed on a 200 g maize oil/kg diet, the phospholipid secretion rate was 1·5 times higher than that observed with a 70 g maize oil/kg diet (Boquillon & Clément, 1979). It has been demonstrated (Juste *et al.* 1983) that in pigs the phospholipid output increases moderately when bile acid output rises sharply, when there is a change from a low- to a medium-level lard diet, whereas the phospholipid output increases much more when bile acid output is in a steady-state, when changing from a medium- to a high-level lard diet. This was interpreted as a possible synergic action between phospholipid and bile acid in the course of biliary lipid adaptation to dietary fat content, resulting in the maintenance of virtually complete dietary fat absorption (Juste *et al.* 1983).

The secretion rate of biliary phospholipids has been shown to be either essentially unchanged whatever the degree of saturation of dietary long-chain triglycerides (Paul & Ganguly, 1976; Juste *et al.* 1983) or it is stimulated by largely unsaturated triglycerides (Redinger *et al.* 1973; Boquillon & Clément, 1979). It is now clear that there is marked increase in the unsaturation of biliary phospholipids as a consequence of eating unsaturated long-chain triglycerides (Paul & Ganguly, 1976; C. Juste unpublished results).

Biliary cholesterol

Increasing dietary fat intake either stimulates (Boquillon & Clément, 1979), or does not alter (Sarles *et al.* 1970; Davis *et al.* 1977) the biliary secretion of cholesterol in rats. It has been demonstrated in pigs that cholesterol secretion rate rises to the same extent whether lard is increased from 20 to 100 g/kg or from 100 to 200 g/kg in the diet (Juste *et al.* 1983). Biliary cholesterol output, however, is the same with 100 or 200 g sunflower oil/kg in the diet, and in this case, much higher than following a lard diet. This, together with the previous conflicting results, suggests that the effect of increasing dietary lipid intake on biliary cholesterol largely depends on the initial level of cholesterol in bile.

The secretion rate, as well as the concentration of cholesterol in bile, is usually higher with diets rich in unsaturated than saturated fats (Boquillon & Clément, 1979; Ramesha *et al.* 1980; Juste *et al.* 1986). However, three research groups have observed constant output of cholesterol in bile following consumption of various diets containing saturated or polyunsaturated fats (Lewis, 1958; Wilson & Siperstein, 1959; Dam *et al.* 1967).

Cholesterol secretion into bile of monkeys was decreased by medium-chain triglyceride supplementation in the studies of Redinger *et al.* (1973).

Relative proportions of biliary lipids: saturation of bile with cholesterol

Since dietary fat may be responsible for unbalanced variations in the secretion of all biliary lipids, one can expect the relative composition of bile and its saturation with cholesterol to be affected too. Despite the great interest shown in the relative composition of bile in relation to diet, disagreement still persists on several points. In particular, dietary fats have been either implicated or disregarded in the determination of bile saturation with cholesterol and the incidence of gallstones. The most commonly accepted view by those who consider fats are involved is an increased saturation of bile and a disposition towards gallstone formation with unsaturated dietary fat (Sturdevant *et al.* 1973; Juste *et al.* 1985). However, some authors have found the effect of unsaturated dietary lipids to be nil (Redinger *et al.* 1973), or even beneficial (Dam & Christensen, 1961) as has been seen after dietary supplementation with medium-chain triglycerides (Redinger *et al.* 1973).

Surprisingly, increasing the lipid content of the diet (whether saturated or unsaturated) has been shown to lower slightly the cholesterol saturation index of bile by Juste *et al.* (1985), while an increased saturation index was reported after a fat-free diet (Dam & Christensen, 1961).

MECHANISMS OF BILE RESPONSE TO DIETARY FAT

Fatty acid length (Malagelada *et al.* 1976; Isaacs *et al.* 1987), intraluminal fatty acid load (Malagelada *et al.* 1976; Hopman *et al.* 1987), and fatty acid saturation (Sarles *et al.* 1960) can all influence gall bladder function and possibly circulation time of the bile acid pool (Gardiner & Small, 1972; Ladas *et al.* 1984), through differential stimulatory effects on cholecystokinin release. According to Malagelada *et al.* (1976), this effect may be mediated through differences in fatty acid absorption rates: the greater the surface area of gut exposed to the stimulus of fatty acid, then the larger the amounts of cholecystokinin released, and the greater the responses of the target organs. Therefore, it was demonstrated that either medium-chain triglycerides (Isaacs *et al.* 1987), or a diet very poor in fat (Hopman *et al.* 1987), or long-chain saturated triglycerides (Sarles *et al.* 1960) were weak stimuli of cholecystokinin release and gall bladder contraction, as compared to long-chain unsaturated triglycerides. However, it is highly unlikely that, with ingestion of diversified dietary constituents (namely proteins and amino acids which are powerful stimuli of cholecystokinin release), differences in hormone levels would persist and could induce an immediate and significant change in biliary lipid secretion rate. Indeed, according to Grundy & Metzger (1972), acute alteration in fat content of a formula infusion did not generally influence the hourly output of biliary lipids, whereas after 2–4 weeks of various fat intakes, clear differences appeared between dietary groups.

In other long-term experiments (Redinger *et al.* 1973; Juste *et al.* 1983, 1986) bile salt secretion rate and pool size have been shown to be related to dietary fat content. Moreover, these experiments strongly suggest that an enhanced pool size is accompanied by increased bile salt synthesis. It was therefore proposed (Redinger *et al.* 1973) that dietary triglycerides would have primary hepatic effects. However, no significant difference in the recycling frequency of the bile salt pool was seen between various long-chain triglyceride supplements, whilst this remained unclear in the case of medium-chain triglycerides. Accordingly, alteration in the bile acid pool size would primarily account for the long-term changes in the secretion rate of biliary bile salts following consumption of various long-chain triglyceride supplements (Redinger *et al.* 1973; Juste *et al.* 1986). The lack of evidence for the involvement of the recycling frequency of bile salts in the biliary response to dietary long-chain triglycerides would appear to be confirmed by the persistence of differences

between diets whatever time of the light–dark cycle was studied (Juste *et al.* 1983). Indeed, if the recycling frequency were responsible for differential secretion rates, the latter would have been essentially limited to digestive periods. Accordingly, dietary fat content would affect the bulk of bile acid absorbed per unit time, without modifying the rhythm of that absorptive activity (Juste *et al.* 1983). Findings obtained from intestinal loops in the rat (Sklan & Budowski, 1977; Fondacaro & Wolcott, 1981) would support our proposition: the rate of transport of the bile acid taurocholate across the jejunal or ileal walls depends on the type and concentration of lipid added to the luminal medium. For each lipid, there seems to be a characteristic 'optimal' concentration for maximal bile acid transport above which bile acid absorption is depressed (Sklan & Budowski, 1977). That could be responsible for the limited increase in bile salt secretion rate in the course of biliary lipid adaptation to dietary fat content (Juste *et al.* 1983).

Since the biliary output of phospholipids and cholesterol is determined by the biliary output of bile salts, modulation of the latter by dietary lipid can be expected to result in alteration of the biliary secretion of phospholipid and cholesterol. However, these parallel changes may be unbalanced, resulting in an alteration in the relative composition of bile and of its saturation with cholesterol. The interrelationships of bile salts, phospholipids, and cholesterol during secretion into bile are then dependent on the level and the nature of lipids in the diet (C. Juste, unpublished results). The biliary phospholipids are essentially derived from a rapidly turning-over pool synthesized in the liver (Kawamoto *et al.* 1980; Barnwell *et al.* 1983), whereas biliary cholesterol is both newly synthesized in the liver and taken up by the hepatocyte from various circulating lipoproteins (Koelz *et al.* 1982; Brown & Goldstein, 1983). This intracellular lipid material could migrate to and fuse with the canalicular membrane which would be continuously damaged by bile salts and then repaired again by new intracellular lipid material (Barnwell *et al.* 1984). Accordingly, complete understanding of the adaptation of biliary lipid to dietary fat content should integrate: (1) the regulation of 'biliary-type' lipid supply in the hepatocyte (phospholipid synthesis and cholesterol synthesis and uptake), (2) the eventual dietary regulation of transport of this intracellular lipid to the canalicular membrane, (3) the extent of lipid material solubilization from the canalicular membrane. The latter implies knowledge of the process of dietary alteration on the relative composition of bile salts and their micellar properties (Barnwell *et al.* 1983), as well as the effect of dietary fat on the lipid composition and fluidity of the membranes (Christon *et al.* 1988). These fields are not yet fully understood.

BILIARY SECRETION AND DIETARY FIBRE

BILE RESPONSE TO DIETARY FIBRE

Choledocal secretion

The relationship between bile secretion and dietary fibre consumption has usually been studied in terms of the fractional lipid composition of bile or bile acid metabolism. Indeed, the total amount of bile and biliary components that are passing through the bile duct to the bowel have been poorly investigated. According to the few studies available, bile flow is either stimulated (Berry-Lortsch & Sable-Amplis, 1981; Ikegami *et al.* 1984; Payne *et al.* 1989; P. Valette & C. Juste, unpublished results), or unchanged (Ikegami *et al.* 1984; Lafont *et al.* 1985) by dietary fibre consumption. It is interesting to parallel the usual choleresis due to dietary fibre and the strikingly high bile flow in herbivores. According to Berry-Lortsch & Sable-Amplis (1981), dietary fibre stimulates both bile acid-independent bile flow, and bile acid-dependent flow through a greater osmotic effectiveness of fibre-

induced bile salt species. The choleretic effect of dietary fibre is not observed after a single dose of high-fibre food (Schneeman, 1979; Ikegami *et al.* 1984), but becomes established progressively over the first week of treatment and remains in a steady state thereafter (Payne *et al.* 1989; Valette *et al.* 1989).

The effect of dietary fibre on the biliary bile salt output is far more complex than on total bile output, and evidence is conflicting. Total bile salt secretion rate has been found to be either increased or unaffected according to the type of dietary fibre (Ikegami *et al.* 1984), to the basal diet used (Lafont *et al.* 1985), to the initial physiopathological state of the subjects (Meyer *et al.* 1979; Berry-Lortsch & Sable-Amplis, 1981), and to the duration of the fibre-enriched treatment (Payne *et al.* 1989; Valette *et al.* 1989). The total bile salt concentration in bile has been observed to be either unchanged (Berry-Lortsch & Sable-Amplis, 1981; Lafont *et al.* 1985; Valette *et al.* 1989), or diminished (Berry-Lortsch & Sable-Amplis 1981; Lafont *et al.* 1985; Payne *et al.* 1989) by fibre consumption.

There are only a few studies dealing with the effect of fibre-enriched diets on cholesterol concentration in bile, and wheat bran was used in nearly all of them. Cholesterol concentration is usually unchanged (Huijbregts *et al.* 1980*a*; Klapdor & Hein, 1982; Lafont *et al.* 1985; Payne *et al.* 1989) and sometimes increased (Lafont *et al.* 1985) after dietary fibre supplementation, provided that the bile is initially unsaturated. The concentration of cholesterol in the bile of lithiasic patients given supplements of bran, however, decreases (Watts *et al.* 1978). In morbidly obese women, however, a diet with a high content of mixed dietary fibres fails to decrease the biliary cholesterol secretion rate (Meyer *et al.* 1979).

Still less is known about the biliary flow of phospholipids; according to Lafont *et al.* (1985) their concentration in bile is not modified by various high fibre treatments.

A series of reports is available on the effects of dietary fibre on the relative biliary lipid composition and lithogenic index. Wheat bran has been used in most studies. It is usually accepted that, when the bile is initially supersaturated with cholesterol, feeding wheat bran (Pomare *et al.* 1976; Watts *et al.* 1978), a concentrated wheat fibre preparation (Marcus & Heaton, 1986*a*), or high-dietary-fibre diets (Thornton *et al.* 1983) results in an improvement in the relative composition of bile. In subjects with normal bile composition, however, wheat bran (Wicks *et al.* 1978; Huijbregts *et al.* 1980*a*), oat bran (Arffmann *et al.* 1983), and purified fibre components (pectin, cellulose or lignin) (Hillman *et al.* 1986) do not further reduce the lithogenic index or alter the relative biliary lipid composition. Also, Huijbregts *et al.* (1980*b*) found that the relative proportions of biliary lipids in vegetarians do not differ significantly from controls consuming a diet relatively low in dietary fibre.

Bile acid pool

The total circulating bile acid pool, whether measured by the isotope-dilution technique in gallstone patients (Marcus & Heaton, 1986*a*) or by the washout technique in pigs (Payne *et al.* 1989) appears not to be altered by dietary wheat bran supplementation. It is, however, slightly increased by a concentrated wheat-fibre preparation (Marcus & Heaton, 1986*a*) and dramatically reduced in morbidly obese women with supersaturated bile, following consumption of a diet with a high level of mixed dietary fibre (Meyer *et al.* 1979).

Schneeman & Gallaher (1980) found that the total amount of bile acids in the overall intestinal contents is elevated in cellulose-fed rats (compared to those receiving a fibre-free diet). However, in rats on a wheat-bran diet, the total intestinal bile acid pool is either unchanged (Brydon *et al.* 1980) or decreased (Sacquet *et al.* 1982*a*). In the former case (Brydon *et al.* 1980), wheat brain supplementation caused an increase in the small intestinal pool and an equivalent decrease in the colonic pool. In the latter study (Sacquet *et al.* 1982*a*), wheat bran had no effect on the small intestinal pool but strongly decreased that

of the caecum and large intestine. Pectin supplementation has no effect on the total intestinal bile acid pool in rats, although a slight decrease was observed in the bile acid pool in the caecum and colon (Sacquet *et al.* 1982*b*).

Accordingly, there is agreement about the lowering effect of dietary fibre on the bile acid pool in the hind gut, and this is much more important with bran (Brydon *et al.* 1980; Sacquet *et al.* 1982*a*) than with pectin (Sacquet *et al.* 1982*b*). However, the bile acid pool was either unchanged (Sheard & Schneeman, 1980; Sacquet *et al.* 1982*a*, *b*), or enlarged (Brydon *et al.* 1980) in the small intestine, by dietary fibre supplementation.

Bile acid metabolism

Most reports on the effects of fibre on bile acid metabolism concern experiments where wheat bran was given. It has rather consistently been found to lead to a decrease in the pool size of deoxycholic acid (Frexinos, 1981; Rigaud & Royer, 1988), and in its relative proportion in bile (Pomare *et al.* 1976; Wicks *et al.* 1978), together with a reciprocal rise in the pool of chenodeoxycholic acid (Pomare *et al.* 1976; Frexinos, 1981), in its percentage in bile (Wicks *et al.* 1978), and in its synthesis (Pomare *et al.* 1976; Frexinos, 1981). This, however, is not observed when the initial fibre intake is high (Wechsler *et al.* 1987). This is consistent with a decrease in the percentage of biliary deoxycholate, lithocholate and total secondary bile acids, and with an increase in chenodeoxycholate observed with cellulose, a major constituent of wheat bran (Hillman *et al.* 1986). However, lignin, another important constituent of bran, appears to have no effect on bile acid composition. This suggested that the effects of bran supplements on bile acid metabolism are likely to be due to their high cellulose content (Hillman *et al.* 1986). This is confirmed by the low biliary deoxycholate concentration seen in some vegetarians (Hepner, 1975) and Nigerians (Falaiye, 1978) consuming high-cellulose diets. As a result, there is a high primary: secondary bile acids ratio in strict vegetarians (Story & Kritchevsky, 1978) or after cellulose supplementation of the diet (Hillman *et al.* 1986). The cholic acid pool and synthesis, however, remained unchanged in lithiasic (Pomare *et al.* 1976) or healthy (Wicks *et al.* 1978) subjects receiving bran, and this is consistent with the stability of cholic acid after feeding major purified constituents of wheat bran, namely cellulose and lignin (Hillman *et al.* 1986).

The effects on bile acid metabolism of a concentrated wheat bran preparation (Marcus & Heaton, 1986*a*) is much less marked than those of native bran. By contrast, pectin, a highly fermentable and gel-forming dietary fibre component, exerts the opposite effects, since it lowers the percentage of primary bile acids in bile, whilst increasing the secondary bile acid deoxycholic acid (Hillman *et al.* 1986).

Accordingly, different fibre components may have essentially opposite effects on bile acid metabolism. This provides possible explanations for the apparently divergent results obtained from some vegetarians (Huijbregts *et al.* 1980*b*), or from populations in the South Pacific (Pomare, 1983) and Africa (Heaton *et al.* 1977) where large amounts of fermentable fibres are consumed.

MECHANISMS OF BILE RESPONSE TO DIETARY FIBRE

Hypotheses have been proposed to explain nearly all the findings on the relationship between bile secretion or bile acid metabolism and dietary fibre. In the following account, however, we shall consider only the mechanisms proposed to explain the well-established effects of dietary fibre on biliary physiology, and will not discuss those mechanisms dealing with still controversial effects of dietary fibre. Accordingly, the depressive effect of dietary fibre on the bile acid pool in the hind gut, the alteration of bile acid metabolism by bran

or its components, the improvement of the lithogenic index of the initially supersaturated biles, and the usual choleretic effect of fibre supplements will be successively discussed.

It has been suggested that an increase in colonic transit time with a low-fibre diet may, in part, account for the larger pool of bile acids in the colon (Brydon *et al.* 1980). This was supported by Sacquet *et al.* (1982*a*) until a relationship between the decreased transit time in the hind gut and the lowered bile acid pool in this part of the gut was clearly demonstrated after consumption of wheat bran (Riottot *et al.* 1984). Moreover, this relationship was assumed to be independent of the fermentation that fibres produce in the hind gut, since the depressive effect of bran on both transit time and bile acid pool size in the caeco-colon does persist in the germ-free rat (Sacquet *et al.* 1982*a*; Riottot *et al.* 1984).

Decreased transit time in the hind gut by wheat bran (Sacquet *et al.* 1982*a*) or cellulose (Hillman *et al.* 1983) could also partly contribute to lower deoxycholic acid, since it would mean less time for 7α-dehydroxylation and for absorption to occur. Marcus & Heaton (1986*b*) found a clear correlation between whole-gut transit time and deoxycholic acid pool size. This was, however, contradicted by Hillman *et al.* (1986) according to whom there was no correlation between intestinal transit time and relative proportion or pool size of deoxycholic acid after cellulose (Hillman *et al.* 1986) or a wheat fibre preparation (Marcus & Heaton 1986*b*). According to Wicks *et al.* (1978), the 4–6 weeks delay in the deoxycholate-lowering action of bran makes it less likely that bran acts chiefly on the absorption of deoxycholate or on exposure time of its precursor to bacteria. Delayed action is easier to reconcile with reduced formation of deoxycholate through metabolic change, namely a fall in the dehydroxylating capacity of the colonic flora. Indeed, according to Hillman *et al.* (1986), the changes in bile acid metabolism induced by dietary fibre were most likely to result from effects on bacterial colonic metabolism. Wheat bran (Hillman *et al.* 1986) and its major constituent cellulose (Huijbregts *et al.* 1980*b*), which are partly fermentable, would lower the colonic pH, resulting in an inhibition of bacterial 7α-dehydroxylation with a resultant decrease in the production of deoxycholic acid. This, in turn, would lift the specific inhibition of chenodeoxycholate synthesis by deoxycholate (Pomare & Low-Beer, 1975) or would diminish the competitive inhibition of chenodeoxycholate absorption by deoxycholate (Hofmann, 1977).

Changes in the relative composition of the bile salt pool may, in turn, influence biliary cholesterol saturation. Increasing the proportion of chenodeoxycholate in the bile acid pool is associated with desaturation of bile and gallstone dissolution (Hofmann *et al.* 1982), whilst deoxycholate may have the opposite effect (Low-Beer & Nutter, 1978). Reduction in the levels of deoxycholic acid or increased chenodeoxycholic acid or both is then the most plausible explanation for the beneficial action of bran on the cholesterol saturation of bile.

Changes in the relative proportion of bile salts appearing in bile could also be partly responsible for the usually enhanced choleresis in dietary-fibre-supplemented subjects, through alteration in their osmotic effectiveness (Berry-Lortsch & Sable-Amplis, 1981). It is, however, highly unlikely that this accounts for the entire effect of fibre on bile flow.

The response of some regulatory peptides to wheat bran consumption has been studied in connexion with concomitant biliary alteration in the pig (Langlois *et al.* 1987; Valette *et al.* 1989). The possible involvement of cholecystokinin and pancreatic polypeptide in biliary changes over the early days of bran consumption can be eliminated. The possible roles of secretin, vasoactive intestinal peptide and even somatostatin, although unlikely (Valette *et al.* 1989), call for further investigation. The non-implication of regulatory peptides in the response of biliary secretion to fibre consumption was previously suggested (but not demonstrated) in two reports, showing that the single administration of fibre (Ikegami *et al.* 1984) or fibre component (Schneeman, 1979) failed to increase bile secretion.

CONCLUSIONS

In the present review, we have shown that dietary changes induce important modifications in pancreatic and biliary secretion physiology.

Pancreatic enzyme biosynthesis shows rapid adaptation to the amount of several ingested dietary components. These changes reach a plateau when a diet is maintained for several meals. The mechanisms involved in such a nutritional adaptation of pancreatic secretion are still unknown. Most authors have suggested that gastrointestinal peptides are the main controlling agents. However, despite a relatively great number of studies, it is not possible to reach a conclusion at present and new methodologies are needed before the picture can be clarified. Very recently, molecular regulation of pancreatic secretion has become the centre of much interest. We believe that knowledge of the molecular steps of enzyme biosynthesis will help reveal the factors involved in pancreatic adaptation to diet. One major and promising area is the description of analogies between the effects of peptides and diets in order to compare them and finally to discover the peptides responsible for adaptation to a specific diet. Simplification of the models through cell culture systems would certainly help in this area.

Concerning biliary secretion, great differences remain on the influence of dietary lipid and fibre, even though a great number of studies have been done, particularly in relation to gallstone incidence and relative bile composition. These divergences could be largely due to actual difficulties in controlling dietary intake in human subjects, to great variations in the initial composition of the basal diets administered to humans or to animals and to the initial physiopathological states of the human subjects. Although most conclusions are limited to a specific context, some general points also emerge.

An increase in dietary long-chain triglycerides usually induces an unbalanced increase in the secretion rate of bile salts, phospholipids and cholesterol in bile and, thus, alteration in the relative composition of bile and its saturation with cholesterol. However, the importance of the lipid dietary source is still debated. Also, most authors agree that dietary fibres have a choleretic effect, with a depressive effect on the bile acid pool in the hind gut, alteration of bile acid composition and improvement of the lithogenic index of initially supersaturated bile in dietary-fibre-supplemented patients.

Mechanisms underlying biliary responses to dietary lipid or fibre have been little investigated and, thus, remain poorly understood. The non-existent or weak direct effect of regulatory peptides is, however, thought significant. Alteration in the bile acid pool through modified bile acid synthesis, intestinal transit, absorption rate and bacterial metabolism is more likely to account for the long-term changes in biliary secretion in response to dietary lipids and fibres, without important involvement of regulatory peptides.

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