CHAPTER 1

General Introduction
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Worldwide, the number of people with diabetes mellitus type 2 (T2DM) is rapidly increasing, especially in South-East Asia (1). T2DM is the most common form of diabetes and characterised by either high fasting or high postprandial blood glucose concentrations or a combination of both (hyperglycaemia) (2). Pre-diabetes is the state before diabetes defined by a high blood glucose levels not meeting the conventional criteria for diabetes, but yet higher than normal (2). Prediabetes is classified into two subtypes: high fasting plasma glucose [Impaired Fasting Glucose] and/or by high 2 hour plasma glucose during an oral glucose tolerance test [Impaired Glucose Tolerance] (2). Lifestyle-related factors such as diet and physical activity can contribute to prevention of T2DM. (3). Repeated exposures to high postprandial glucose (PPG) responses are implicated in the development of pre-diabetes and T2DM (4).

Reducing PPG by slowing the rates of carbohydrate digestion seems to reduce the progression from pre-diabetes to T2DM (5-7). This is indicated by studies with the drug acarbose (5, 8) and from meta-analyses and reviews of studies with low glycaemic index (GI)/glycaemic load diets (6, 7, 9, 10).

The most effective way to turn starchy foods into more-slowly digestible versions and the post-absorptive effects of this are still not well understood. The present research was undertaken with four aims:

1. To investigate how starchy foods can be made more slowly digestible
2. To predict the rate of digestion (in vitro methods)
3. To study the impact on the PPG and associated insulin (PPI) responses in humans
4. To understand the associated glucose fluxes and metabolic mechanisms and their implications for health

In this introduction chapter some basic terminology in the area of starch digestion, absorption and glucose metabolism and regulation will be discussed. The technology of in vitro digestion and dual stable isotope technique used in in vivo studies will also be addressed. In addition some aspects of pathophysiology will be discussed.

1.1. Carbohydrates: basic terminology, classifications and chemistry and their influence on digestion

Dietary carbohydrates are a diverse group of substances with a wide range of chemical, physical and physiological characteristics (11). Dietary carbohydrates should be classified according to their chemical form, i.e. the individual monomers, degree of polymerization (DP) and type of linkage (alpha or beta), as recommended at the 1997 FAO/WHO Expert Consultation (12). This divides carbohydrates in three main groups: sugars (DP 1-2; mono- and
disaccharides), oligosaccharides (short-chain carbohydrates) (DP 3-9) and polysaccharides (DP ≥ 10) (11). In addition to the chemical description, a physical description of dietary carbohydrates is also important. The crystalline state, association with other molecules such as protein, lipid and divalent cations and aggregation into complex structures in cell walls are important for the availability of starch. The solubility, water holding capacity, viscosity and gel formation, binding and adsorptive capacity and fermentability are important determinants of the action of dietary fibres under gastrointestinal conditions (13, 14).

Neither chemical nor physical descriptions of carbohydrates can fully predict their range of physiological effects and health implications. The most important physiological division within carbohydrates is whether they are bio-available (can be digested by human intestinal enzymes, so-called glycaemic carbohydrates) versus bio-unavailable carbs (such as dietary fibre and resistant starch) (11). Starch consists of amylopectin, comprised of glucose chains with frequent branching, and amyllose which is characterized by very few branches (15). Resistant starch is the sum of starch and products of starch digestion (such as maltose, maltotriose and alpha-limit dextrins) that have not been digested in the small bowel (16). Resistant starch (RS) can be divided into different types reflecting the source of resistance to digestion: RS1 is due to physical barriers to digestion, RS2 to ungelatinized starch granules, RS3 to retrogradation, RS4 is chemically-modified starch and RS5 is lipid-complexed starch (17). All dietary fibre definitions (including CODEX) identify dietary fibre as carbohydrate polymers and oligomers materials that escape digestion in the small intestine and pass into the large intestine, where they are slightly or nearly completely fermented (18). There is some evidence that legume flour can lower the PPG due to its higher content of resistant starch (19) and high concentration of slowly digestible starch (20).

The main factors which determine starch digestibility are the intrinsic starch characteristics such as the amylose/amylopectin ratio, intactness of the grain and the botanical source (21). In addition, processing factors also play an important role in starch digestibility (22). Processing factors such as cooking, baking and cooling determine the blood glucose response via intermediate processes such as gelatinization and retrogradation. Gelatinization is the collapse (disruption) of molecular order (breaking of H-bonds) within the starch granule manifested in irreversible changes in properties such as granular swelling, native crystallite melting, loss of birefringence and starch solubilisation during hydrothermal treatment (23). On the other hand, retrogradation is the recrystallization of the amorphous phases created by gelatinization, into double helical crystalline structures (24) when amyllose is available (25).
Dietary fibres can also have an impact on digestion, depending on the nature of the fibre. Non-viscous fibres do not have an effect on digestion. For example, wheat bran does not reduce glycaemic response or digestibility in bread (26). Especially viscous soluble fibres can reduce starch digestion and absorption in the intestine due to viscosity formation under gastrointestinal conditions (27).

1.2. Starch digestion, absorption and fermentation

- **Chewing and digestion of starch in the mouth**
  The role of the mouth in digestion is to grind food into a more homogenous, softer mass (bolus) that can be swallowed and pass through the oesophagus to the stomach (28). Lingual alpha-amylase is secreted during oral digestion, and may even survive gastric conditions to exert its effect in the stomach and small intestine (29). However, it is uncertain whether this salivary amylase has any significant effects on starch digestion, because the digestion process is dominated by the action of pancreatin (30). The estimation is that some 15% of total starch in a meal is digested by lingual alpha-amylase (5% in the mouth and 10% in the small intestine) (31). Nevertheless, a study by Ranawana (32) showed that the GI of starch-rich products (rice) is increased by the degree of mastication (32).

- **Gastric emptying (GE)**
  An important role of the stomach is to control the rate of nutrient delivery to the body through the regulation of GE (33). GE is an important determinant of the rate of entry of glucose into the systemic circulation (34) and therefore the PPG response (35), given the rapidity and completeness of absorption of glucose and other monosaccharides in the small intestine (36). The rate of GE has been shown to account for ~35% of the variance in PPG levels after glucose loads and following intake of solid carbohydrate-containing meals in healthy individuals (35) and in patients with T2DM (37).
  Gastric emptying is regulated by both gastric factors (characteristics of the ingesta) and to a greater extent by duodenal factors (feedback effects) (38). Gastric factors include food volume, caloric content (39), acidity, fluid viscosity, and food physical properties such as texture and density (40). For example GE is controlled in such a way that contents are delivered to the duodenum at about 2.3 kcal/min (39) though a more recent article gives a wider range of 2-4 kcal/min (38). Duodenal receptors which regulate GE respond to distension, the presence of acid, carbohydrate, fat and protein digestion products, and osmolarity differences from that of plasma (41). Prevailing blood glucose levels also regulate GE, such that acute elevations of blood glucose levels slow GE and GE is accelerated during hypoglycaemia (42). Viscous fibres (43) or gel-
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forming fibres (e.g. alginate) (44) can delay GE resulting in a decreased PPG response. The interplay between incretins, GE and blood glucose is discussed further under “Glucose metabolism and regulation”, in a subparagraph on hormones involved.

- **Intestinal digestion of starch**
  The major hydrolysis products from the intraluminal phase of starch digestion are maltose, maltotriose and other fragments containing alpha-1,6 bonds (alpha-limit dextrins) (31). These sugars and short oligosaccharides are hydrolyzed to glucose by two dual-enzyme protein complexes, maltase-glucoamylase (MGAM) and sucrase-isomaltase (SI), in the brush border of the small intestine. All four enzymes represented in the 2 complexes are exohydrolytic, thus hydrolyze alpha-1,4 and alpha-1,6 linkages from non-reducing ends of glucose oligomers and polymers (45), the difference being their degree of specificity for particular glycosydic linkages at the nonreducing termini of alpha-glucans (46). SI displays more hydrolytic activity on branched alpha-1,6 linkages than MGAM. MGAM substrate specificity somewhat overlaps with that of SI (47).

- **Glucose absorption across intestinal wall**
  The glucose resulting from MGAM and SI hydrolysis is transported across the intestinal mucosa. Glucose absorption across the intestinal brush-border membrane is predominantly mediated by SGLT1, a membrane protein that couples two molecules of Na+ together with one molecule of glucose, although glucose transporter type 2 (GLUT2) may also play a role especially in higher luminal glucose concentrations (48).

- **Carbohydrate fermentation in the colon**
  The overall capacity of the human body to digest and absorb bio-available carbohydrates is very high (at least up to 300g starch per meal) (49). In healthy individuals, significant amounts of material arrive in the colon only when the carbohydrates are indigestible or partly indigestible (as is the case with e.g. resistant starch, sugar alcohols and fructo-oligosaccharides). The indigestible carbohydrates will be fermented by the colonic microbiota into short-chain fatty acids (SCFAs) and gases (hydrogen (H2), carbon dioxide and methane) (31). H2 is absorbed and mostly excreted in expired air. The degree of this so-called colonic spillover can be measured by H2 in breath (50) which is used as a qualitative indicator of carbohydrate arrival and fermentation in the colon. The fermentation of indigestible carbohydrates can be accompanied by borborygmi and flatulence at low doses and at higher doses by painful symptoms like bloating, cramps and abdominal pain (51).
1.3. *In vitro* starch digestion models

There are a number of *in vitro* protocols varying in complexity that model different aspects of carbohydrate digestion (52, 53). One of the purposes of using *in vitro* models is for screening carbohydrates (e.g. legume flours) and/or dietary fibres for their potential digestibility and glycaemic effects when incorporated in a food format (pre-clinical testing). In addition, these models can be used for innovation for research and development and for getting more mechanistic insights. However, these models cannot cover all phases of starch digestion described in section 1.2 and cannot replace human clinical testing. Furthermore, for predicting glycaemic responses, a major limitation is absence of any post-absorptive components (e.g. reflecting insulin release and glucose disposal). Separate models are also available for fermentation (54).

- **Static versus dynamic models**

The intestinal digestion models can roughly be divided into static (e.g. Englyst model) (53) and dynamic models. The Englyst method is based on an *in vitro* enzymatic method to determine the response of food carbohydrates to enzymatic digestion (53). Starch that is hydrolyzed within 20 min is designated rapidly digestible starch (RDS), and that which releases glucose within 20-120 min is slowly digestible starch (SDS), while starch that is not hydrolyzed after 120 min is identified as RS (53). The *in vitro* estimates of starch digestibility by the Englyst method has been shown to be qualitatively predictive of post-prandial blood glucose concentrations for many foods (55).

An example of a dynamic model, which includes both chemical and physical breakdown in the stomach as well as the intestine, is the TIM-Carbo model as described by Bellman et al (52). Dynamic mechanical models of digestion have an advantage over static models, as they allow for examination of both physical and chemical breakdown of food products during the different digestion steps. However, these models are more complex in design and fabrication and, as is the case for all models, always require validation with human clinical data (56).

- **Enzymes involved**

The standard Englyst method uses the combination of porcine pancreatin and fungal glucoamylase (53) and these were also used for our *in vitro* flat bread digestion assay (57). However, fungal glucoamylase directly converts starches and alpha-amylase hydrolysates to glucose (58). In humans *in vivo* as noted previously, this requires the action of mucosal alpha-glucosidase together with alpha-amylase.
1.4. **Glucose metabolism and regulation**

This section describes the underlying metabolic mechanisms (i.e. organs and hormones involved) involved in the regulation of PPG. In addition, glucose fluxes are discussed, because they eventually make the distinction possible between the origins of the glucose (e.g. glucose from food versus from the liver) and ultimately determine the PPG response.

- **Glucose as fuel**

  Glucose is the key energy substrate for life. All human cells can metabolize glucose through glycolysis and tricarboxylic acid cycle coupled with mitochondrial respiratory chain to synthesize adenosine triphosphate (ATP) (59). It is the preferred fuel for the brain and the nervous system, which can also survive on ketones (60). The rate of glucose utilization by the brain is estimated to be 117-142 g/day (61).

- **Hormones involved**

  Insulin and glucagon are two opposing hormones central in the regulation of glucose metabolism. By modulating the relative concentrations of glucagon and insulin the pancreas is able to respond homeostatically to high and low blood glucose levels (62). Insulin is secreted from beta-cells of the pancreas and is stimulated by glucose, amino acids (especially branched-chain) and gastrointestinal hormones (such as the incretin hormones (next paragraph), and secretin, gastrin and cholecystokinin) (62). Insulin facilitates transport of glucose from the bloodstream into peripheral tissues such as skeletal muscle and adipose tissue (63). It regulates the translocation of intracellular vesicles containing the GLUT4 glucose transporters to the plasma membrane by binding to the insulin receptors on skeletal muscle cells and adipocytes. After fusion the GLUT4 transporters are able to transport glucose into the cells (64). In addition, insulin encourages biosynthesis of proteins, inhibits the production of glucose by the liver and lipolysis and free fatty acid efflux from adipose tissue (62).

  The insulin response to an oral glucose load is three- to fourfold greater than observed after an “isoglycaemic” intravenous infusion of glucose (65). This so-called incretin effect led to the discovery of hormones, secreted from the gastrointestinal tract in response to nutrients that stimulate insulin secretion in a glucose-dependent manner (66). The two known incretin hormones are glucose-dependent insulino tropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) and together they account for up to 60% of the postprandial insulin response in healthy humans (67). They are an important regulating factor in glucose homeostasis (68). GIP secretion from K cells in the upper small intestine is enhanced in response to ingestion of meals or glucose (69). GLP-1 is released by the L-cells in the ileum and secretion is potently stimulated by
glucose, fatty acids and essential amino acids and other endocrine hormones, as well as neurotransmitters (70). The length of the small intestine exposed to carbohydrate is an important determinant of GLP-1 release (71). Poorly absorbed carbohydrates (e.g. tagatose) which probably expose a greater length of gut to nutrients, result in delayed GLP-1 secretion but not in delayed GIP release (72). GLP-1 for example can delay GE which acts to sustain the release of nutrients over time into and from the small intestine (73). In addition, GLP-1 and GIP together, inhibit beta-cell apoptosis and promote beta-cell proliferation, thereby expanding pancreatic beta-cell mass, while GIP enhances postprandial glucagon response under certain circumstances and GLP-1 suppresses it (74). GIP has no effect on glucagon responses during hyperglycaemia, while strongly potentiating insulin secretion. In contrast, GIP increases glucagon levels during fasting and hypoglycaemia, when it has little or no effect on insulin secretion (75). In adipose tissues, GIP but not GLP-1 facilitates fat deposition (74). GLP-1 and GIP exert their effects by binding to their specific receptors, the GIP receptor (GIPR) (76) and the GLP-1 receptor (GLP-1R) (77). Secreted GIP and GLP-1 are rapidly degraded by Dipeptidyl peptidase-4, which diminishes the insulinotrophic effects of these hormones (78).

Glucagon is secreted from alpha-cells in the pancreas in response to hypoglycaemia (79) and its secretion also rises following increases in circulating levels of amino acids and fatty acids and response to adrenergic stimulation and to some regulatory peptides (80). Glucagon mobilizes stored nutrients, increases glycogenolysis and gluconeogenesis, and promotes lipolysis (62). Another glucoregulatory hormone is amylin, which is produced by the beta-cells and co-secreted with insulin (81). Amylin improves postprandial blood glucose levels by suppressing GE and glucagon secretion and a synthetic analogue of human amylin is used as an anti-diabetic drug (82). Amylin was not taken into account in our research, because there was not a good analytical method available.

- Organs involved

The amount of glucose in plasma is tightly regulated, because of harmful effects of low or high glucose levels. Many organs are involved such as the liver, muscles, adipose tissue and intestine. The liver has a central role in the regulation of systemic glucose and lipid fluxes during feeding and fasting (83). In short-term starvation glucose is derived from 1) glycogenolysis, the release of glucose from stored glycogen in the liver (84) and from 2) gluconeogenesis (85), i.e. the de novo formation of glucose from common metabolites in the body such as amino acids, glycerol, lactate, pyruvate and intermediate metabolites of the citric acid cycle (84).
Under longer-term fasting conditions (e.g. overnight), circulating glucose is mainly derived from gluconeogenesis, because of depletion of glycogen stores. In these conditions a high influx of NEFAs derived from adipose tissue lipolysis generates an abundance of ATP and reducing equivalents that sustain the conversion of pyruvate and other intermediates (e.g. gluconeogenic amino acids) into glucose (83).

In the fed state there is an abundance of different nutrients in the portal vein, together with high levels of insulin, which promote hepatic glycogen synthesis and under specific circumstances de novo lipogenesis (DNL), while fatty acid oxidation and endogenous glucose production are suppressed (86). Glycogen synthesis and glycogenolysis can occur simultaneously in the liver, so-called ‘glycogen cycling’ (87). Skeletal muscle is the largest site for insulin- and exercise-stimulated glucose disposal and utilization (88). The intestine can contribute to the control of glucose homeostasis via its high glucose utilization capacity (89). Recently a novel function of intestinal glucose metabolism (gluconeogenesis) has been described and suggests the intestine contributes to about 20-25% of total endogenous glucose production (90).

- **Measuring postprandial glucose and insulin**

  PPG response can be measured in venous and capillary blood. Venous blood gives a lower PPG response than capillary blood (factor ~0.67) (91, 92), because the tissue will consume glucose and the glucose concentration in the peripheral vein will be lower than in the artery (93). Capillary blood is a mixture of arterial and venous blood. Another measure of postprandial glucose response is the GI, which is the ratio of the glycaemic response (capillary blood, +iAUC for 2 hours) of 50g of available carbohydrates of the test food and glycaemic response of reference food (glucose or bread) (93). Insulin is normally measured in serum and another measure is the insulinaemic index, which can be determined in the same way as the glycaemic index (94).

- **Glucose fluxes: why are they important and how can they be measured**

  In many studies PPG response to different foods has been measured and where it is relatively low, it has been assumed that this is because the process of digesting and releasing the glucose from that food is slow (95). However, the PPG response also reflect rates of glucose disposal and endogenous production. Only the use of stable isotopes can really determine whether there is a slower digestion, as shown by a delayed influx of $^{13}$C labelled glucose units in the food (96). In practice, a dual stable isotope technique is necessary to distinguish between glucose originating from the meal and the glucose from the liver.
The dual tracer method utilizes two distinct glucose tracers that can be differentiated analytically, e.g., [U-$^{13}$C] in the meal and [6,6-$^{2}$H$_{2}$] glucose infused intravenously (97). Glucose fluxes are then calculated using Steele’s non-steady-state one compartment model (98). The rate of appearance of total glucose (RaT) is calculated from isotopic dilution of the infused glucose tracer. The rate of appearance of oral or exogenous glucose (RaE) is calculated from the rate of appearance of ingested glucose tracer and the glucose tracer enrichment of the meal. The endogenous glucose production (EGP) is then calculated by subtraction of RaE and the infused glucose from RaT (97). The rate of disappearance of total glucose (RdT, also called glucose disposal) is the total amount of glucose which is taken up by the tissues. The RdT can be calculated from the glucose clearance rate (GCR) and the glucose concentrations. The GCR can be calculated from the non-steady-state elimination rate of the infused tracer.

- **Pathophysiology**
  The potential pathophysiological mechanisms of actions of hyperglycaemia are an increase in 1) flux in the polyol pathway, 2) formation of advanced glycation end-products, 3) protein kinase C activation and 4) flux through hexosamine pathway leading to vasoconstriction, inflammation and thrombosis (99). It is important to know which pathways are mostly involved in the pathophysiological aspects of a high glucose load.

1.5. **Study questions and outline**
Carbohydrate-rich staple foods are key candidates for reducing PPG exposures. This thesis comprises information on how to delay the absorption of carbohydrates in staple foods and how this delay in absorption will cause further post-absorptive effects, as reflected by changes in various flux parameters and levels of gastrointestinal hormones.

The following specific questions were addressed:

1. **How can starchy staple foods be made more slowly digestible?**
2. **How can the rate of digestion be predicted in an *in vitro* assay?**
3. **What is the impact of the slowly digestible staple foods on PPG and PPI in humans?**
4. **What are the associated glucose fluxes and metabolic mechanisms and their implications for health?**
To answer these questions, the following subquestions are defined.

1. **How can starchy staple foods be made more slowly digestible?**
   1.1 *How can rice characteristics and processing methods applied to rice influence the post-prandial glycaemic and insulinaemic responses?*
   We performed a systematic review to elucidate which rice characteristics and processing methods influence PPG and PPI, by summarizing and evaluating the results from randomized controlled trials with diverse varieties of rice around the world. In addition, post-harvest processing (such as parboiling) and consumer processing were also taken into account (Chapter 2).

   1.2 *How can food hydrocolloids influence post-prandial blood glucose response?*
   In a narrative review we explained how food hydrocolloids are able to lower blood glucose response. One of the important characteristics of food hydrocolloids is their viscosity under gastrointestinal conditions, and we discuss which characteristics of the hydrocolloids are responsible for the level of viscosity. We also discuss mechanisms independent of viscosity by which food hydrocolloids could influence PPG (Chapter 3).

2. **How well does an *in vitro* digestibility assay, specifically adapted for flatbreads, predict the observed *in vivo* results in this product format?**
   We developed an *in vitro* digestibility assay based on the method of Englyst, but modified to reflect more realistic physiological conditions (including an oral digestion step, optimization of the intestinal pH and amount of digestive enzymes). In addition, a statistical model was developed for estimating the *in vitro* rate of starch digestibility (k) based on the Chapman-Richards model. In a regression model variables of *in vitro* starch digestion were correlated with the *in vivo* plasma glucose response (Chapter 4).

3. **What is the effect of guar gum in combination with chickpea flour incorporated in flatbreads on the PPG and PPI response?**
   The insights on viscous fibres and different starches were applied for slowing the rate of starch digestibility in optimized food products. In this series of human clinical trials South-Asian flatbreads were used as the optimized food products, because they are important carbohydrate-rich staple foods for a sizable population and therefore important contributors to their glycaemic load (Chapter 4).
3.1 How much do the individual viscous fibres guar gum and glucomannan alone or in combination with chickpea flour contribute to the PPG lowering effect of South-Asian flatbreads?

The effect of South-Asian flatbreads, varying in the levels and combinations of viscous fibres (guar gum and konjac mannan) with or without chickpea flour were initially examined in healthy Caucasian subjects in a balanced incomplete block design. We assessed the effect on PPG. (Chapter 4).

3.2 What is the effect of guar gum (2-4%) in combination with chickpea flour incorporated in flatbreads on the PPG and PPI response in an Indian population?

Based on the results in an exploratory study (Chapter 4), we tested the effect of additions of specific combinations of chickpea flour with lower doses of GG added to a flatbread flour mix, for their impacts on PPG and PPI responses in a South-Asian population (Chapter 5).

4. What are the glucose fluxes and metabolic pathways associated with the PPG-lowering interventions we tested?

4.1 What is the effect of guar gum in combination with chickpea flour incorporated in flatbreads on the rate of appearance of exogenous glucose (RaE) and on the other fluxes (endogenous glucose production (EGP) and rate of disappearance of total glucose (RdT))? In earlier studies, we saw an effect of high-fibre flatbreads on PPG and presumed that the influx of glucose was delayed due to the viscous fibres. To test this we executed a study using the dual stable isotope technique to differentiate between the different glucose fluxes. In addition, we assessed the insulin and incretin responses and examined their association with the different fluxes (Chapter 6).

4.2 What is the effect of a change in the rate of influx of glucose from the intestine on the PPG, PPI and EGP and RdT?

Up to now, it has been largely assumed a delay in digestion of carbohydrates only or mainly leads to a reduced PPG by a reduced RaE, but the actual quantitative contribution of RaE and the other glucose fluxes (EGP and RdT) was not clear. We therefore performed a systematic review and a meta-analysis of human clinical studies with $^{13}$C-labelled carbohydrate substrates to quantify the effect of variation in the rate of uptake of exogenous glucose (RaE) on PPG and PPI responses and to estimate the effect of a change in RaE on the other flux parameters EGP and RdT (Chapter 7).
4.3 What is the effect of guar gum in combination with chickpea flour incorporated in flatbreads on $^{13}$C-glucose metabolites?

We showed that slowing of digestion not only led to a reduced influx of glucose, but also to a reduction in uptake of glucose into the tissues. By metabolomic analyses we assessed the different $^{13}$C-glucose metabolites derived from samples of the earlier dual stable isotope study to identify whether the delay in glucose influx induced by a fibre mix altered specific metabolic pathways related to the disposal and metabolism of glucose in the tissues and endogenous glucose production (Chapter 8).
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