Diet and health

THE ROLE OF THE INTESTINAL MICROBIOTA IN METABOLIC DISEASES

BIOCODEX
Microbiota Institute

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1 • A WIDE RANGE OF DISEASES

Every day cascades of chemical reactions take place in our body in order to keep us alive: it is the metabolism. Unbalanced by ways of living to which it is no longer adapted (excess salt, sugar and fat, sedentary lifestyle…) obesity, diabetes and cardiovascular diseases are wreaking havoc across the planet. Still unsuspected just ten years ago, the involvement of bacteria of our intestinal flora in these modern world diseases is however proving crucial.

What are the links between intestinal microbiota and metabolic diseases[1,2]?

If our cells require the right fuel to carry out their various functions, this is also the case for our intestinal bacteria: the multiple essential roles they play in our great metabolic symphony have only recently been discovered. Watch out for harmful effects in the event of wrong notes…

Our intestines are home to a common base of bacteria mainly divided into two large groups: the *Bacteroidetes* and *Firmicutes*; the former being more abundant than the latter when we are healthy. However, in obese individuals, the balance tilts towards the *Firmicutes*. These bacterial species are thought to extract more calories from the food that we ingest–in particular complex sugars–than the *Bacteroidetes*, leading to excess weight.

A vicious circle of inflammation

Then, an entire cascade of "bad" reactions of the organism is activated by a diet that is too high in fat which unbalances the intestinal microbiota. The barrier function of the intestines is no longer as effective; they are less resistant and let through molecules produced by the bacteria. This triggers an abnormally persistent and silent response from the immune system. The pancreas is impacted by this chronic inflammation and produces less insulin, which in turn is less well used by

1 Pascale A, Marchesi N, Marelli C, Coppola A, Luzi L, Govoni S, Giustina A, Gazzaruso C. *Microbiota and metabolic diseases.* Endocrine. 2018 May 2. doi: 10.1007/s12020-018-1605-5

2 Li X, Watanabe K, Kimura I. *Gut Microbiota Dysbiosis Drives and Implies Novel Therapeutic Strategies for Diabetes Mellitus and Related Metabolic Diseases.* Front Immunol. 2017 Dec 20;8:1882. doi: 10.3389/fimmu.2017.01882

METABOLIC DISORDERS IN A NUTSHELL

- They disrupt the metabolism, i.e. the biochemical reactions which allow cells to obtain their food and produce energy, and the organism to get rid of its waste
- They can be present at birth or develop later in life due to certain factors (poor diet…)
- The most common are obesity, diabetes and hypertension

our cells leading to insulin resistance, a characteristic of type 2 diabetes. Storage of fats in the tissues and their transport in the blood are also disrupted. The blood vessels are not just obstructed by fat, but also dilate less effectively. Finally, a cardiovascular bomb made up of abdominal fat, elevated blood lipids, high blood pressure and hyperglycemia leads straight to what is called metabolic syndrome.

The guardians of our metabolism

Conversely, in the case of a diet that is beneficial for our intestinal flora like the Mediterranean diet (diet rich in fruit, vegetables and olive oil, and low in meat), a virtuous mechanism is set in motion: our bacteria produce short-chain fatty acids (SCFA), a source of energy for our cells. These SCFA are involved in the regulation of appetite, bowel movements and the formation of fats. They can act on insulin production and blood pressure. Some, like butyric acid, protect the cells of our intestines from inflammation and help them fight against aggressive microbes. They are even thought to have anti-cancer properties. Not to mention the fact that bacteria produce vitamins (K, H and B) and help us to absorb calcium, magnesium, vitamin D and iron. Some researchers no longer hold back from stating that the intestinal microbiota is an organ in its own right.

IN FIGURES

THE INTESTINAL MICROBIOTA IN FIGURES[1]

70%
of total microbiota
Average weight: 1.5 kg

100 trillion
microorganisms (bacteria, fungi, viruses, parasites)

500 to 1,000
species

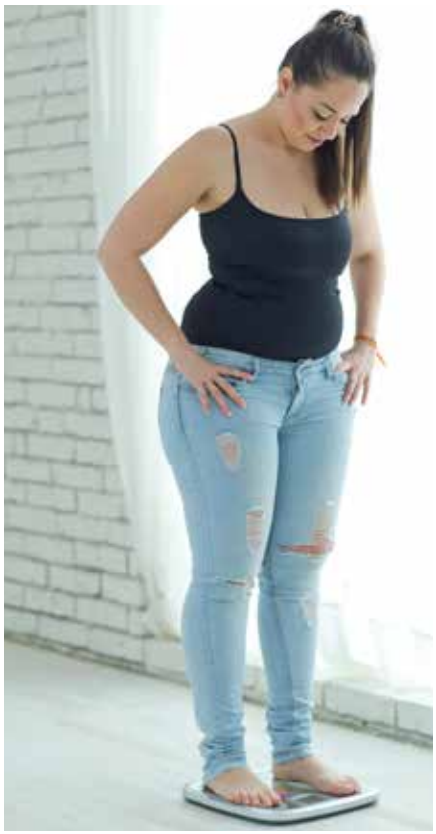
250 to 800
times more genes than human DNA

Focus on diabetes[3]

Diabetes could become the 7th highest cause of death in the world by 2030 according to the WHO, bringing its share of strokes, amputations, blindness and dialysis. A scourge which could be partly combatted by a healthier lifestyle... and perhaps by working on our intestinal flora, provided that we can unravel its multiple actions on our metabolism.

It has been known for a long time that diabetes is associated with sugars. However, it is also associated with intestinal bacteria which enable us to digest slow sugars (starch and other dietary fibers) by breaking them down into simple sugars which ferment into short chain fatty acids (SCFA) and, inevitably, gas. However, individuals with type 2 diabetes are thought to have a microbiota less rich in bacteria that produce these famous SCFA. Other bacteria have less beneficial effects: they cause chronic inflammation of the liver through accumulation of fats (the famous "NASH", or non-alcoholic steatohepatitis). Some also release toxic substances when they die, whose presence in the blood is associated with an increased risk of diabetes. Furthermore, as 90 to 95 %

3 Harsch IA, Konturek PC. *The Role of Gut Microbiota in Obesity and Type 2 and Type 1 Diabetes Mellitus: New Insights into "Old" Diseases.* Med Sci (Basel). 2018 Apr 17;6(2). pii: E32. doi: 10.3390/medsci6020032



of diabetics are also obese, they suffer from the chronic inflammation found in obesity, partly generated via the intestinal microbiota.

Bacteria which tilt the balance

In type I diabetes, where the immune system turns against the pancreatic cells responsible for insulin production (beta cells), the composition of the microbiota changes: a flora less rich in *Proteobacteria* and overabundance of *Firmicutes* relative to *Bacteroidetes* are thought to be some of the risk factors. Conversely, some bacteria (lactobacilli, bifidobacteria, bacteria that produce butyric acid) could provide protection against autoimmunity, a deregulation which forces us to fight against our own immune defenses. Finally, there are also other members of the microbiota– i.e. viruses–such as Coxsackie viruses[4] that are capable of infecting the insulin-producing cells of the pancreas.

On the track of elucidating treatment mechanisms

To complicate matters, bacteria are also thought to influence the actions of metformin. This drug used in first line treatment of type 2 diabetes is thought to reduce the inflammation caused by toxic bacterial substances while reducing the absorption of fats... *via* the intestinal flora. This might shed light on its mode of action which is still unclear, but could also bias the results of studies conducted in these patients. These are all mechanisms among many others which link diabetes and the intestinal microbiota, whose vast and complex field of action we are barely beginning to discern.

4 Exclusively human viruses belonging to the enterovirus family (which reproduce in the intestines)

Types of diabetes

Diabetes is a disease characterized by an excessively high level of glucose in the blood (hyperglycemia). There are two main types.

TYPE I DIABETES		TYPE 2 DIABETES
Autoimmune disease which leads to the destruction of the insulin-producing cells of the pancreas. It affects approximately 10% of diabetic individuals	**Definition**	Metabolic disorder marked by reduced sensitivity of cells to insulin caused by lifestyle (obesity, sedentary lifestyle ...). It represents around 90% of diabetic individuals
Intense thirst, pronounced general fatigue, frequent urination	**Symptoms**	Frequent absence of symptoms, especially in the first years
Injection of insulin	**Treatment**	Improved lifestyle (physical activity, balanced diet...); injection of insulin

Source: Inserm

2. DIET: A KEY FACTOR

Fat? Our taste buds love it and are regularly drenched with it, to the detriment of our intestinal flora, which then succumbs to the Dark Side of inflammation and weight gain. Unless we choose good fats and do not skimp on fibers. A more balanced diet which would be tempting to tailor to each individual, if only our florae were not so diverse...

Eating too much fat unbalances our intestinal flora[5,6]

Hyperglycemia, hyperlipidemia, hypertension: the effects of a diet that is too high in fat are known but they are only the tip of the iceberg. Researchers have thoroughly disclosed the major role of the intestinal microbiota in these metabolic disruptions. They also sorted the good fats from the bad.

The same observation is made in laboratory mice given a high fat feed as in patients with metabolic syndrome: their intestinal flora does not resemble that of their healthy counterparts: too much fat on a daily basis reduces the amount of *Akkermansia muciniphila*, a beneficial bacterium which improves glycemia and insulin sensitivity, and protects against the formation of fatty plaques in the vessels (atherosclerosis). As its name indicates, this bacterium also produces a substance called "mucin", which strengthens the protective mucus of the intestinal barrier. Another side-effect of excess dietary fat: lactobacilli and bifidobacteria, "good" bacteria which reduce inflammation and formation of adipose tissue, are decreased.

Not all fats are the same

But incidentally, which fats are we talking about? Saturated fatty acids like palm oil are indeed to be avoided, as is hammered home by public health messages: they are associated with lowered bacterial diversity and weight gain. Conversely, the oleic acid contained in olive oil, a monounsaturated fatty acid of the omega-9 family, is thought capable of restoring bacterial diversity and of reducing weight –in mice at least. We should also rely on omega-3 polyunsaturated fatty acids, such as fish oil, which promote the presence of *Akkermansia muciniphila*, lactobacilli and bifidobacteria. These omega-3-containing foods should moreover take precedence over those containing omega-6, which are also essential to the organism but are to be consumed with moderation as they cause inflammation and a reduction in bifidobacteria.

5 Yang BG, Yeon Hur KY, Lee MS. *Alterations in Gut Microbiota and Immunity by Dietary Fat.* Yonsei Med J 2017 Nov;58(6):1083-1091. doi : 10.3349/ymj.2017.58.6.108

6 Cândido FG, Valente FX, Grześkowiak ŁM, Moreira APB, Rocha DMUP, Alfenas RCG. *Impact of dietary fat on gut microbiota and low-grade systemic inflammation: mechanisms and clinical implications on obesity.* Int J FoodSci Nutr. 2018 Mar;69(2):125-143. doi: 10.1080/09637486.2017.1343286

“First and foremost, eat your fiber”

And as fat doesn’t do everything, good or bad, another food category also carries weight with respect to metabolism: fibers. Those indigestible sugars present in cereals, tubers, nuts, seeds, fruits and vegetables. Without fibers to ferment to extract their energy in the form of SCFA, bacteria begin to snack on the protective mucus which lines our intestinal cells, exposing them to bacterial invasion. Moreover, fibers enable better control of glycemia, probably through the presence of *Prevotella* in our intestines. Conclusion: for your microbiota, eat fat without excess–but good fat–and don’t forget your fibers!

Dietary sources of fatty acids

Fatty acids are fats.
Their classification depends on their chemical structure.

SATURATED

- Plant sources: ready meals, palm oil, pastries, biscuits, sauces…
- Animal sources: butter, cheese, crème fraîche, fatty meats…

Their consumption in excess promotes weight gain and the occurrence of cardiovascular diseases.

UNSATURATED

- **Monounsaturated**
  Omega-9: olive oil, hazelnut oil
- **Polyunsaturated**
  Omega-3: fatty fish (salmon, tuna…), fish oil, rapeseed oil
  Omega-6: groundnut oil, sunflower oil…
- **Trans**
  Fatty acids with various origins (natural, technological or formed during cooking): processed products, margarines, pizzas, quiches…

Consumed in moderation, mono and polyunsaturated fatty acids contribute to the proper functioning of the cardiovascular system.

Their consumption in excess fosters cardiovascular diseases and a rise in “bad“ cholesterol.

Sources: National Health Nutrition Program, ANSES

Diet and treatment: a history of microbial inequality[7]

"Miracle" diets do not exist, and this also applies to the bacteria of our intestinal flora. The prolific diversity of our microbiotas, shaped by our dietary behaviors, might explain why some individuals respond better than others to improved dietetics.

Show me your daily menus and I will tell you what your microbiota looks like: our diet has a massive influence on our intestinal flora, and researchers have been able to draw up standard profiles of intestinal microbiotas. You have a sweet tooth? The chances are that your flora contains a predominant amount of *Prevotella*, which would improve control of glycemia. Fan of animal protein and saturated fats? You will be rather the *Bacteroides* type, exposed to an increased risk of colon cancer. You prefer brown rice to white rice? You probably harbor fewer proinflammatory enterobacteria. Then, would the recipe for metabolic happiness be to order our intestinal flora through what we eat?

Unpredictable diets

Unfortunately not, as we are not equal in terms of the positive effects of a balanced diet. It is the fault of our intestinal microbiotas, none of which resembles another in all aspects, even in twins. Hence the impossibility of predicting with precision the effects of a dietary intervention on our intestinal bacteria. A flora naturally rich in *Lactobacillus* will absorb more probiotics after two weeks of consuming fermented milk. Similarly, a microbiota richer in *Prevotella* before a three day "diet" of barley bread (high in fiber) helps to better control glycemia compared to microbiotas less well endowed with this bacterial species. Taking into account these individual variations, a diet low in FODMAPs[8] could have more or less success with bloating and abdominal pain depending on the initial composition of the intestinal flora.

Some florae are more resilient than others

Eating more fibers will be all the more beneficial for our level of bifidobacteria if we have already consumed it regularly beforehand. Finally, some microbiotas may show themselves more resistant to a change in diet; a resilience which can prove counterproductive in the context of nutritional regulation. The use of algorithms capable of integrating all of this interconnected data is one of the avenues being studied to direct the remodeling of our flora by means of diet. For the moment, and before researchers manage to simultaneously integrate all these parameters at the level of a single individual (dietary habits, composition and resilience of the intestinal flora), a personalized modulation of the microbiota still remains a challenge.

7 Healey GR, Murphy R, Brough L, Butts CA, Coad J. *Interindividual variability in gut microbiota and host response to dietary interventions.* Nutr Rev. 2017 Dec 1;75(12):1059-1080. doi: 10.1093/nutrit/nux062

8 Oligosaccharides, disaccharides, monosaccharides and fermentable polyols: non digested sugars but fermented by our intestinal bacteria

3. WHAT ARE THE THERAPEUTIC PROSPECTS?

To lighten the global burden of metabolic diseases, we would need to be able to make a large part of the planet adopt healthier dietary habits. A necessary but difficult task. Simultaneously, interventions at the heart of intestinal bacterial dynamics are under consideration: will probiotics and fecal microbiota transplants be the great new metabolic therapies of tomorrow?

Probiotics at the service of "fatty liver" syndrome[9]

Far from being a French specialty, "fatty liver" syndrome (foie gras in French) is driving up the number of hepatitis cases all around the world. Research is turning with increasing seriousness towards probiotics to stem these new epidemics. And the gamble seems to have paid off.

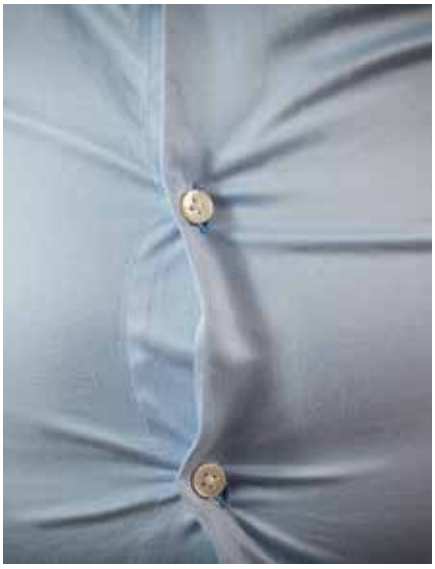
Cases of viral, alcoholic, and now increasingly fatty, hepatitis are soaring due to obesity and type 2 diabetes. Excess fat accumulates in liver tissue, first causing non-alcoholic hepatic steatosis (NAFLD[10]) which can escalate into non-alcoholic steatohepatitis (the famous NASH[11]), itself heralding cirrhosis–point of no return for the liver. As in obesity and type 2 diabetes, the intestinal microbiota plays a frontline role. Hence the hope of countering this overdose of fat through probiotics: an avenue followed with success by research for around ten years.

From animals to humans

The first studies in animal models proved the benefits of using probiotics and prebiotics, and even synbiotics (a combination of the two). By way of example, the addition of fructooligosaccharides to probiotics led to a reduction in inflammation and in fatty particles in the liver, loss of weight and fat mass, and improved insulin sensitivity in some patients. These positive results were confirmed by the decrease in fat content of the liver in Hong Kong patients treated for six months with a mixture of lactobacilli and bifidobacteria. Decreased liver stiffness–a sign of diminished aggression–was observed in Iranian patients after taking synbiotics for twenty-eight weeks.

A convincing trial by the book

An additional step forward has been taken in establishing probiotics as a valid therapeutic option through a clinical trial conducted in a few dozen Ukrainian patients with non-alcoholic hepatic steatosis. The daily administration of a probiotic containing fourteen living strains over an eight week period produced a clear reduction in hepatic fat, some inflammatory markers and enzymes indicative of a diseased liver. These effects remain to be confirmed in a larger number of patients and over the long-term. But probiotics look very promising in the fight against these overdoses of fat for which our livers pay the price.



9 Kobyliak N, Abenavoli L, Mykhalchyshyn G, Kononenko L, Boccuto L, Kyriienko D, Dynnyk O. *A Multi-strain. Probiotic Reduces the Fatty Liver Index, Cytokines and Aminotransferase levels in NAFLD Patients: Evidence from a Randomized Clinical Trial.* J Gastrointestin Liver Dis. 2018 Mar;27(1):41-49. doi:10.15403/jgld.2014.1121.271.kby

10 *Non-Alcoholic Fatty Liver Disease*

11 *Non-Alcoholic Steato-Hepatitis*

Fecal transplant: a promising route?[12]

This will surprise more than one person: using stool for therapeutic purposes did not start yesterday. But recent discoveries regarding the involvement of the intestinal bacteria in metabolic diseases have opened up a new field of research which aims to develop fecal transplants that are more targeted and better accepted clinically and psychologically.

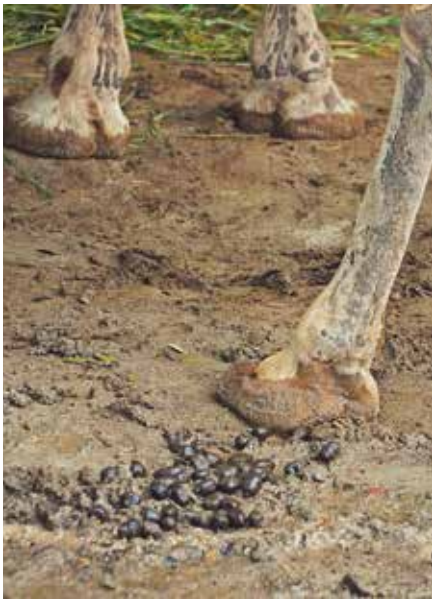
Fecal Microbiota Transplant (FMT): a name which is redolent of innovation and the biotech world. However, it was used 1,700 years ago in China, where diarrhea was treated by drinking a broth of fermented stools–the aptly named "yellow soup". In the Middle Ages, the Bedouins protected themselves against dysentery (a bacterial infection causing serious diarrhea) by ingesting the droppings of their camels. The first modern fecal transplants were performed in the 1950s to combat *Clostridium difficile* infection, a bacterium which takes advantage of the microbial imbalance triggered by an antibiotic treatment to proliferate within the intestinal flora. We had to wait until the 2000s for FMT to be taken into account in the treatment of metabolic diseases, and in the cages of laboratory rodents.

Conclusive first steps

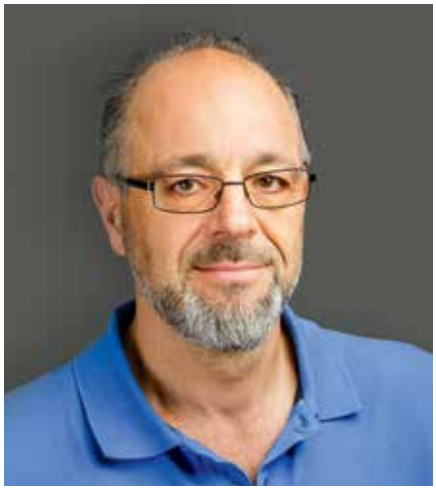
But trials in humans in this field are just beginning. The first study was carried out in 2012 in Dutch patients: half of them received the stools of healthy donors; the others received their own stools (placebo group). The donor stools were analyzed carefully to eliminate any risk of infection by viruses, parasites or harmful bacteria. Then the transplant took place over a thirty-minute period by injection into a tube, introduced into the noses of patients, which opened out into the small intestine. Six weeks later, those who received "healthy" stools exhibited improved insulin sensitivity and increased numbers of bacteria producing metabolically beneficial butyric acid. This first attempt can thus be counted as a success!

A *modus operandi* to be refined

The use of FMT in metabolic diseases still has a long way to go, with many challenges to be faced: the medical history and the microbiotas of donors must be irreproachable to avoid any transmission of diseases and strains chosen in an appropriate manner and in the right quantity. Other issues: how will the donor flora be welcomed by that of the recipient? Will a single injection be sufficient for long-term colonization? Finally, a considerable psychological limitation: the inevitable repulsion of some patients in the face of this still little-known treatment, unless FMT becomes a common therapeutic practice, knowing that its spectrum of potential applications could extend to multiple sclerosis, Parkinson's Disease or chronic fatigue syndrome. Who knows? Perhaps the future will see the advent of stool banks and capsules.



12 de Groot PF, Frissen MN, de Clercq NC, Nieuwdorp M. *Fecal microbiota transplantation in metabolic syndrome: History, present and future.* Gut Microbes. 2017 May 4;8(3):253-267. doi: 10.1080/19490976.2017.1293224



Professor Rémy Burcelin is the Head of a laboratory that specializes in the study of the mechanisms at work between the brain, intestines and the rest of the body, at the Institute of Metabolic and Cardiovascular Diseases (Inserm Unit/Paul-Sabatier University Toulouse III). His team is one of the pioneers of the discovery of the involvement of the intestinal microbiota in the management of sugar and fat by our organism.

Can we hope to cure metabolic diseases one day by the intestinal microbiota route?

In the 21st century, a new organ was discovered: the intestinal microbiota. This is why probiotics–which act on our flora–give us great hope. It is however too soon to consider probiotics as an independent therapy at the moment: they are likely to partially correct metabolic diseases. But firstly, patient groups with defined characteristics (biological and socioeconomic) must be isolated. Then the presence of certain bacteria as diagnostic biomarkers must be identified. And finally, extensive clinical trials must be conducted in accordance with precise objectives (lowering glycemia for example). Candidate bacteria are under consideration but for the moment none have been sufficiently effective; in particular none have shown efficacy in weight loss. But, in the current state of research, we could see probiotics arriving on the market to prevent diabetes in ten years or so.

What obstacles need to be overcome to develop an "à la carte" management of the microbiota?

The technological barriers have been eliminated thanks to real advances such as the development of effective algorithms capable of analyzing large amounts of data. The limitations are elsewhere: on the one hand, in the capacity to be able to cultivate and identically reproduce a bacterial strain (a living product, therefore perishable) once it has been identified as potentially effective; on the other hand, regulatory aspects when dealing with organisms that are liable to spread as an epidemic. For if some bacteria have proven to be harmless over the long term, others recently identified require more perspective. In any event, individual variability is not necessarily a constraint: treating just 1% of obese patients would already be a phenomenal success.

What avenues still remain to be explored in microbiota research?

Probiotics as treatment boosters. In 2017, our team showed in mice that the microbiota increases the activity of GLP-1, an intestinal hormone that is part of the therapeutic arsenal of type 2 diabetes, to which some patients are resistant. Other prospects could come from dietary fibers and polyphenols (found in grapes and pomegranates), two elements which allow positive modulation of the microbiota; or their combination with minerals, or other agents active in what is called "cobiotics". Last avenue: aiming at a synergistic effect with synbiotics (combination of probiotics and prebiotics). These are interesting strategies to improve the tolerance and efficacy of treatments.

"WE COULD SEE PROBIOTICS ARRIVING ON THE MARKET TO PREVENT DIABETES IN TEN YEARS OR SO."

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