SAFE HEALTH REPORT

Scientific Data … Informed Choice … Actionable

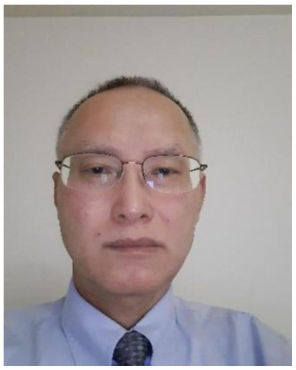
November 2022 *Official Newsletter for MrGineaPig* *Issue 4*

Please repeat once before proceeding: **He Can Do It, She Can Do It, I Can Do It!**

Inside …

Human Microbiome

Your Ticket to Exuberant Health for the next 5 years



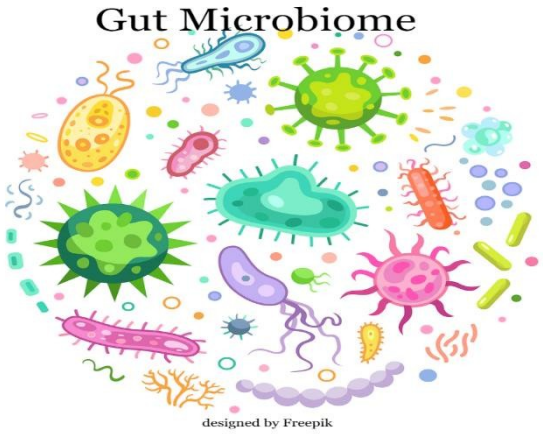
Ike Kim, Editor

Microbiome is a term used to describe microbes (bacteria, fungi, viruses) in our gut especially in large intestine. There are 100 trillion of these microbes weighing about 5 pounds in our gut as compared to 10 trillion cells in entire human body. They outnumber human cells by 2:1 and microbial genes outnumber human genes by 200:1. Scientists did not pay attention to microbiome until late 1990s. Bacteria in microbiome help regulate immune system, produce B vitamins cyano-cobalamin, ribo-flavin, thiamine and Vitamin K. The gut microbiota provides the fermentation of non-digestible sub-strates such as dietary fibers and intestinal mucus.

What does microbiome have to do with health?

Bacteria in our gut, skin and elsewhere appear to be essential for human immune function and nutrition.

Laura Grieneisen and her colleagues describe nearly universal inheritability of gut microbes in the Journal



Science in July 2021. She shows 97% of microbiome phenotypes were significantly heritable when controlled for diet, age, and socioecological variation. It appears one

inherits more microbe genes than genes from mother. Autoimmune diseases appear to be passed in families not by gene inheritance but by inheriting the family's microbiome. In fact, early fecal transplantation, a life-saving procedure, for patients with relapsing infection with bacteria, Clostridium difficile was done from mother to daughter.

So, then the importance of human microbiome, as first suggested in 2001 by Joshua Lederberg, who coined the term "microbiome, to signify the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space" cannot be overstated as it affects one's susceptibility to infectious diseases and contributes to chronic illnesses. In fact, microbiome research is so important that National Institutes of Health, research-granting arm of the US government, allocated estimated $913 million dollars in 2022 from zero dollars in 2018. In short, human life is not sustainable for any extended period without the help of microbiome.

Food preference – is it bacterial or human preference?

Neuroscientist found out that the gut microbiome communicates with the brain and influences food choices. Carols Ribeiro and his colleagues showed that essential amino acids

and the concerted action of the gut bacteria Acetobacter and *Lactobacilli* are critical modulators of food choice in their journal article that was published in PLOS Biology on April 25th, 2017. In their study, three groups of fruit flies were fed one with sucrose with all the essential amino acids, second group with sucrose with some of the amino acids, and third group with sucrose solution but took out one amino acid at a time to determine which amino acid gut microbiome could not live without. In 72 hours, all three groups were fed with protein-rich yeast. Group 2 and 3 with restricted amino acid diet exhibited strong cravings for the yeast to compensate for the missing protein nutrients. They then identified five different gut microbiota and fed these bacteria to group 2 and 3. Although deficient in essential amino acids, group 2 and 3 did not crave for more protein. Despite the flies in groups 2 and 3 getting more of those bacteria in their diet, they still had low levels of amino acids and still were able to reproduce. The importance of the finding is that the gut microbiome communicates with the brain and influences the choice of food whether it is protein-rich food or protein-deficient food.

More recently, Zeng and colleagues quantified inputs and outputs of the mouse gut microbiome using isotope tracing. In their Cell journal article published on July 20th, 2022, they described bacteria in Firmicutes phylum preferred dietary protein, Bacteroides dietary fiber, and Akkermansia circulating host lactate. Main finding was that diet shapes the composition of microbiome in the host gut when given their preferential food.

Main take-home message from these two pivotal studies is that bacteria in our gut communicates to our brain via dopamine-like neurotransmitters to have

the host consume more high fat and high sugar containing food. This in turn further promotes the growth and composition of undesirable bacteria such as Proteobacteria while decreasing beneficial bacteria such as Bacteroidetes. By making dopamine-like neurotransmitters, these 'bad' gut bacteria make us feel good and happy. This is endless loop where the 'bad' bacteria are serving its own interest at the expense of the host. But all is not lost. While the bacteria in our gut may dictate to our brain which food to consume, we can change the gut bacterial flora composition intentionally by changing what we eat, i.e., feeding the food that are preferred by beneficial bacteria.

It appears the one of best way to change microbiome in our gut is by not only changing the food that promotes beneficial bacteria but also adding prebiotics and probiotics simultaneously. It is now well-known even human relationship compatibility may be dependent on microbiome composition especially after course of antibiotics.

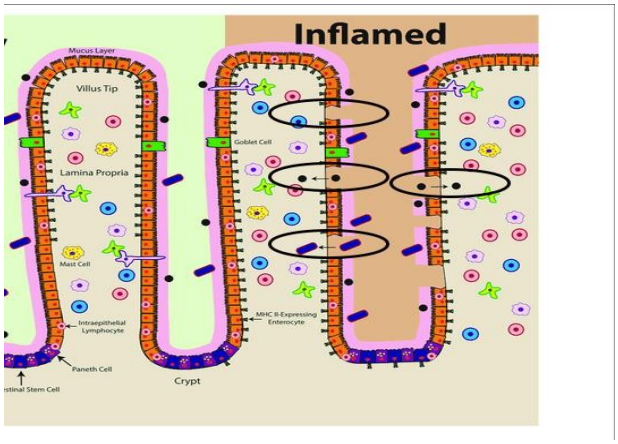
Leaky gut syndrome

What exactly is human gut? Our gastrointestinal is only thought of simply performing digestion with the help of microbiome. But it turns out it's much more that. Gut contains more nerve cells than entire spinal column with more computational power than much-studied spinal cord. Further, two thirds of human immune system is contained within the gut. We used to think microbiomes stay on their side of gastrointestinal wall and we stay on our side. Nothing could be further from the truth. Intestinal epithelial cell, the outermost layer of intestine, is a single cell layer that form the surface lining of both small and large intestine. How frightening is that reality? It's single cell layer that separates human body from outside world. No wonder majority of human immune system is contained in the gastrointestinal tract. The constant interplay of 100 trillion cells in the microbiome and human immune system is only beginning to be unfolded. For example, tuberculosis in the lung sends a signal to gut immune cells to kill of certain microbiome.

Leaky gut syndrome is a medical condition characterized by altered intestinal hyperpermeability brought about by decreased levels of tight junction proteins, increased concentrations of proinflammatory cytokines, and changes microbiome changes. It is postulated many of human autoimmune diseases have origins with leaky gut syndrome.

The left side of Figure 1 below depicts pink mucus protective layer continuously produced by gut immune cells and red single cell layer of enterocytes that are joined together by tight junctions. The right side of the picture shows black rectangular bacteria and little circular bacterial biproducts that pass right through leaky holes in inflamed intestine.

Figure 1. Leaky holes denoted by black circles



*Adapted from Wosen et al 2018. Frontiers in Immunology. 2018: 9:2144. Under creative Commons License 4.0 on 10_19_2022.

The movement of bacteria and its biproducts from their side across the red defense line of enterocytes to our side is called translocation. There are different kinds of infections that follow when this defense line is compromised, including bacteremia (blood infection), bacterial peritonitis (infection of peritoneum). Actual bacteria do not need to cross the enterocyte cell line in order to cause internal systemic effect. In fact, only bacterial biproducts called endotoxins needs to cross over the mucus and then the enterocyte layer to cause profound physiological response in the form of hypotension or low blood pressure with a subsequent risk of acute renal failure. It's more acutely demonstrated in patients with liver disease.

Lipopolysaccharide (LPS) of gut microbiome denoted by little circular dots cross into the bloodstream and aggravate low-grade inflammation and insulin resistance.

In summary, imbalance is intestinal microbiome not only causes leaky gut syndrome but also chronic systemic inflammation that is known to cause insulin resistance and obesity.

Types of gut microbiome

It is generally accepted that a fiber-rich diet causes increased intestinal motility, increased satiety, better glucose and cholesterol control. While fiber is indigestable by the human gut, microbiome utilizes it and cross-feed the gut epithelium with secondary metabolites. Individual dietary patterns along with antibiotic use largely determines one's composition of microbiome. About 90% of microbiota of health individuals are made of bacteria phyla, Firmicutes and Bacteroidetes and the remaining 10% is made up of organisms from other phyla such as Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia. These bacteria consume nutrients and produce beneficial short chain fatty acids (SCFA), vitamins B and K, various secondary polyphenolic degradaton products that impact the host. Three short chain fatty acids from dietary fiber, acetate, propionate and butyrate, play important roles in host homestasis. A higher ratio of Firmicutes to Bacteroidetes is a biomarker for metabolic syndrome including obesity; this high ratio also increases with older age.

- ✓ **Avoid high fat high sugar diet that causes high ratio of Firmicutes to Bacteroidetes**
- ✓ **High ratio of Firmicutes to Bacteroidetes is related to obesity**
- ✓ **Avoid foods that favor growth of Proteobacteria that produces lipopolysaccharides (LPS)**

Probiotic: Bacillus subtlis:

Probiotics are "live microorganisms that are intended to have health benefits when consumed" according to National Institute of Health. These live bacteria are found in yogurt and fermented foods such as miso, sauerkraut, yogurt, kimchi, pickles, kefir, kombucha, tempeh, sourdough bread and some cheeses. These live organisms include bacillus, lactobacillus, Bifidobacterium and Saccharo-myces boulardii. We will start probiotic coverage with Bacillus.

Bacillus subtilis is a Gram-positive, rod shaped that forms heat-resistant dormant spores. It is found in soil, roots of plants and in aquatic environments and not considered to be a human pathogen. Bacillus subtilis along with other Bacilus species is classfied by FDA to be "generally regarded as safe". It is widely used in biotechnology and up 60 of commercial enzymes are produced using Bacillus subtilis. It is considered to be an

universal cell factory for microbial production of chemicals, enzymes, and antimicrobial materials.

This remarkable bacterium produces 7 different antibiotics and is replacing virginiamycin – a standard antibiotic similar to pristinamycin and quinupristin/dalfopristin that is used in about 70% of poultry production. Due to increasing consumer awareness of antimicrobial resistance and food safety, virginiamycin is being either banned or restricted in South, Korea, US, European Union.

Further, Rhayat et al in 2019 published the effect of *Bacillus subtilis* strains on intestinal barrier function and inflammatory response in the Journal, Frontiers in Immunology. One of the findings was an experimental Bacillus subtilis strain, Bs 29784, significantly reinforced intestinal barrier integrity under basal conditions through an up-regulation of the expression of tight junction proteins in chickens. These are the proteins needed to maintain tight junctions of the intestine.

Of the same genus Bacillus, Bacillus coagulans was shown to modulate human microbiome as reported by Maity et al (2020) in the Journal of Dietary Supplements. Bacillus coagulans was added to fecal samples obtained from pre- and post-treatment of irritable bowel syndrome (IBS) patients. The authors found there was positive up-regulation of phyla such as *Actinobacteria* and *Firmicutes* and down-regulation Bacteroides, Proteobacteria, Streptophyta and Verrucomicrobia.

Choosing Probiotics

Most non-enteric coated probiotics do not survive acidic gastric pH. For example, only 5.3% of bifidobacteria are reported to survive through the gastrointestinal transit while only 0.1% for Lactobacillus gasseri does so. In addition, both Lactobacilli and Bifidobacteria do not form significant population even with sustained oral intake and the effect of increased beneficial bacterial count usually dissipates within 2 days of stopping the supplement. Consumers are advised to choose probiotics that are enteric coated since probiotics are acid-labile except for Bacillus species. Bacillus species form spores that are heat-stable and acid-stable and do not need the aid of enteric coating.

Take Home Lesson:

- ✓ **Taking Bacillus class of probiotic may be beneficial in preventing leaky gut syndrome.**
- ✓ **Choose enteric coated probiotics or Bacillus type of probiotic**
- ✓ **Bacillus coagulans (Schiff Digestive Advantage) would be an example. Note: Safe Health Report does not endorse any products.**

Natto: A Japanese infatuation with Bacillus subtlis – will be aired on Safe Health Report YouTube Channel

Case Number 4. Can this 51-year-old male be saved at least next 5 years?

Case examples present real life patient cases from the ground floor as we send these folks to palliative care or hospice care settings. Frailty score is often considered when making major placement decisions to optimize patient care. It is also used to see whether patient can withstand major surgical interventions. It is due to poor frailty score that patients often do not survive 5 years after major health crisis.

Thomas Gillin is a 51-year-old male with type 2 diabetes now on diabetic

medications glipizide, metformin, and insulin regimen as well as atorvastatin for cholesterol, and amlodipine/carvedilol for high blood pressure. He has recently undergone right shoulder rotator cuff surgery. He has recently been diagnosed with benign prostate hypertrophy for which he is taking tamsulosin. His blood pressure is 145/90, heart rate of 82. Just looking at the Eye of Tiger test and ADL score, his chance of living next 5 years looks promising but not guaranteed since uncontrolled diabetes can progress rapidly with life-altering macrovascular complications such as coronary artery disease, peripheral arterial disease, and stroke and microvascular complications such as kidney failure, blindness, and limb amputations.

Eye of the Tiger Test for Thomas Gillin

*All patient data is fictional. Safe Health Report complies fully with US HIPPA regulations.

Clinical Frailty Score

- **1 – Very Fit: Very fit for their age with no disease symptoms, very active and exercise regularly- 5 days a week**
- **2 – Fit: Still no active disease as in 1 but exercise only occasionally – three times a week or only seasonally**
- **3 – Managing Ok: Disease symptoms are well managed. Not able to exercise at all other than walking.**
- **4 – Very Mild Frailty: Symptomatic disease. Not dependent on others for daily activities but disease symptoms slow down their activities. May need cane for walking occasionally for example**
- **5 – Mild Frailty: Symptomatic disease limit daily activities. Needs walkers. Needs help with walking and shopping.**
- **6 – Moderate Frailty: Needs helps with walking, shopping, climbing stairs, bathing with disease progression.**
- **7 – Severe Frailty: Completely dependent for personal care and daily activities but seem stable and at risk of death within the next 6 months.**
- **8 – Very Severe Frailty: Same as 7 but unstable and even mild illness is likely to cause death.**
- **9 – Terminally Ill: As in 8 but not likely to live next 3-6 month.**

*Adapted from Rockwood & Theou 2020

Thomas Gillin's Frailty Score 3

Thomas Gillin

*All patient data is fictional. Safe Health Report complies fully with US HIPPA regulations.

Age: 51
Sex: .....Male
Weight: .....220 pounds
Height: .....5 feet 7 inches

Activities of Daily Living (ADL) components: transfer, bed mobility, toileting, and eating

- **0 – Independent: If the resident completed the activity with no help or oversight every time during the 7-day prior period.**
- **1 – Supervision: If oversight, encouragement, or cueing was provided three or more times during prior 7 days.**
- **2 – Limited Assistance: If resident was highly involved in the activity and received physical help in guided maneuvering of limb(s) or other non-weight-nearing assistance three or more times during the last seven days.**
- **3 – Extensive Assistance: If resident performed part of the activity over the prior 7 days, help of the following type(s) was provided three or more times: ▪ Weight-bearing support provided three or more times. ▪ Full staff performance of activity during part, but not all, of the prior 7 days.**
- **4 – Total Dependence: If there was full staff performance of an activity with no participation by the resident for any aspect of the ADL activity. The resident must be unwilling or unable to perform any part of the activity over the entire prior 7-day period. ▪ 7 – Activity occurred only once or twice: If the activity occurred but not 3 times or more. ▪**

8 – Activity did not occur: If, over the prior 7-day period, the ADL (or any part of the ADL) was not performed by the resident or staff at all. ADL support measures the most support provided by staff over the prior 7 days.

*Adapted from Minnesota Department of Health Guideline

Thomas Gillin's ADL Score 2

It seems disease(s) find us as one gets older no matter how much one tries to hide. At any rate, this gentleman is asking for help with losing weight. We will discuss first on simplified summary of obesity and the difficulty of addressing weight in diabetes.

Obesity

Current guidelines attribute obesity to excess calorie intake and not enough exercise following the principles of thermodynamic laws. In fact, NIH guidelines from 1980s, namely avoiding too much saturated fat and including adequate starch and fiber has not made any dent in obesity epidemic. There are so many 12-week course of various diets with

claims of guaranteed results. We really have to stop pretending there is a magical formula for weight loss.

In short, there are a very short-term, medium term and long-term control of energy intake and expenditure by the human brain via satiety hormones such as GLP-1 (glucagon-like peptide 1) and PYY (peptide tyrosine tyrosine), and the hunger hormones, such as ghrelin. For the short-term, when ghrelin levels in the blood rise, hunger sets in, and with food intake, ghrelin levels start dropping off and the satiety hormones GLP1 and PYY start rising, signaling satiety, and stopping further food intake.

In the medium term, leptin, a protein made by fat cells, signals to the brain an estimate of fat needed in the body over the longer term whether to increase or decrease body fat. Recent gut microbiome studies suggest that certain bacteria may cause additional calorie extraction from the food intake and store them as fat. For the medium term, brown fat (discussed in October Issue) 'consumes' the energy rather than storing it. Some people are born without any leptin due to inheritance of genes, hence brain fails to take action in response to accumulating fat. Most people with obesity are resistant to the action of leptin and have very high levels of leptin. Examples of genetic origin of obesity not only include leptin deficiency but also pro-opiomelanocortin (POMC) deficiency. These two conditions need medical therapy; changing diet will have very little effect.

As human evolution has it, the enzyme, lipoprotein lipase (LPL) which is present in in fat and skeletal muscle cells, facilitates triglycerides into those cells. The Entry of triglycerides (TG) into skeletal muscles cells leads to "burning" of TG for energy production while entry into fat cells cause TG to be stored as body fat. In winter months, LPL activity in fat cells increases in favor of energy storage and to provide fat for insulation over the long winter. How to drive LPL activity into skeletal muscle cell is $64,000 question. Exercise is what increases LPL activity in the skeletal muscle cells. As you can see human body is designed for under-fed conditions but not for over-fed conditions.

- ✓ **Summary, obesity may have nothing to do with being a couch potato.**
- ✓ **Obesity is truly a medical condition.**
- ✓ **Human body is designed for under-fed conditions.**

Obesity and Diabetes

What is insulin? Insulin serves an anabolic hormone responsible for proper storage of nutrients following ingestion of a meal. Insulin coordinate along with glucagon to modulate blood glucose levels. It regulates glucose levels in the bloodstream and induces glucose storage in the liver, muscles, and adipose tissue, resulting in overall weight gain.

Specifically, insulin promotes lipo-genesis, resulting in the storage of triglycerides in cells specialized in the storage of fat (adipocytes) and production of low-density lipoproteins (LDL) in liver cells (hepatocytes) thus causing cardiovascular sequalae. Obesity, diabetes and cardiovascular disease are metabolic diseases that are linked together.

In short, when one takes insulin shots, glucose enters one's cells. This makes the sugar levels in the blood go down. This is the goal of all insulin treatment. One can think of insulin as elevator button. Once pressed, the elevator arrives and loads up the glucose and delivers the glucose to cell's power plant called mitochondria, numbering anywhere from 1000-1500 per individual cell. At the same time, oxygen is delivered to smallest blood vessels called capillaries where oxygen is released and diffuses into mitochondria where 'combustion' can occur much like gasoline engine. It is from these cellular reactions called oxidative phosphorylation (Ox Phos) that energy is released in the form of ATP. Obviously, you would need a thermostat (thyroid) to regulate body temperature which also controls Ox Phos. In obesity, red blood cells are known to clump together in narrowed blood vessels not able to release oxygen as readily. Even the smallest decrease in oxygen to mitochondria would have a significant effect since 95% of oxygen is utilized by mitochondria in a human body.

Going back to Mr Gillins case, he has a very worthy goal. While on the insulin regimen, it would be extremely difficult for him to lose any weight as he would be swimming upstream against the current.

First recommendation would be to see an endocrinologist to assess whether he could be transitioned to non-insulin diabetic regimen and also to assess whether his obesity is from genetic disorder including any thyroid disorders.

Second recommendation is to institute dietary changes that decreases the production of newly discovered obesogen, a gut bacterial metabolite. Of the seven major metabolites of intestinal bacterial origin, delta-valerobetaine has been found to be the most important obesogenic. Ken Liu and his colleagues from Emery in December 2021 describe their findings in the journal, Nature Metabolism. Liu et al. discovered a microbially manufactured metabolite, delta-valerobetaine (VB), impaired mitochondrial fatty acid β-oxidation.

This metabolite was also shown to elicit upregulation of downstream genes of peroxisomal proliferator-activated receptor alpha (PPARα), which was puzzling given the role of PPARα in promoting lipolysis. This beneficial effect of delta-valerobetaine was reversed with the feeding of a high fat and sugar "Western diet". When delta-valerobetaine, given intravenously to humanized mice, is combined with high fat and high sugar Western diet, it led to an increase in perigonadal visceral adipose tissue, posterior subcutaneous adipose tissue, and interscapular brown adipose tissue, as well as exacerbated hepatic steatosis.

His team was able to show VB reprograms hepatic lipid and mitochondrial metabolism. His team showed that people who are obese or have liver disease tend to have higher levels of delta-valerobetaine in their blood. Tri-methyl-**lysine**, a precursor to VB, is high in red meat. Therefore, any diet high in lysine could theoretically increase the levels of delta-valerobetaine and should be avoided. Delta-valerobetaine itself is also a precursor of trimethylamine N-oxide already shown to be associated with cardiovascular diseases. This study was of monumental importance in understanding obesity and intestinal biome. We will delve into further into microbiome discoveries by screening 297 journals

devoted to the new scientific field of metabolomics with more than 35,800 articles published since 1998 when metabolome was first coined.

Take Home Lesson

- ✓ **Weight loss may be easier with non-insulin medical therapy.**
- ✓ **Change diet from high fat, red meat and lysine to diet rich in fiber that produces short chain fatty acids from beneficial microbiome.**
- ✓ **Does hyperinsulinemia cause obesity which then cause insulin resistance? Or obesity simply cause insulin resistance as traditionally believed? What are the ramifications for weight loss? Stay tuned!**

Safety Tip 1: For Catfish Lovers

Catfish in the US is mostly Vietnamese origin with more than 90% market share. Swai and Basa catfish are commercially raised in Mekong River basin, one of the most polluted rivers on earth. Many consider the Swai and Basa fillets a delicacy, as they are wider and thinner in appearance than the US counter parts. Chances are you will be eating one of these imported catfish if you order catfish from any of the U.S. restaurants. Less than 2% of the imported catfish is inspected by the US FDA. This is not to imply US counterpart is any better. US aquatic fisheries use antibiotics very widely to increase fishery yield. There are case reports of anaphylaxis with fish allergies in the medical literature. One of the patients with fish allergy had an anaphylaxis with levofloxacin, which was used to treat patient's pneumonia in author's experience.

- ✓ **If you have had prior experience of anaphylaxis with any catfish or any fish, please do not rechallenge yourself since you are not likely to survive!**

Safety Tip 2: For Meat Lovers

Sodium or potassium nitrates and nitrites are used as preservatives in meat packing industry and gives it aesthetically pleasing look. When an animal is slaughtered in meat packing plant, the meat turns to brown color due to blood coagulation, not a red color! Nitrites keep meat red by bonding to the myoglobin and acting as a substitute for the oxygen. These are also common preservatives used in cured meat products including bacon, deli meat, and jerky. It has been linked to the development of heart disease and diabetes. If exposed to extreme heat as in cooking or a highly acidic environment as in our stomach, sodium nitrate can change into nitrosamine in the body. Nitrosamine is a known carcinogen. This author was surprised to find out adding these preservatives is still the standard today as it was some 40 years ago when the author was working in butcher shop as a high school student.

- ✓ **Wash off the red dye and pop a vitamin E capsule and smear on the meat prior to grilling.**

MrGineaPig's Core Long-Term Trial

LONG-TERM TRIAL	SUPPLEMENT	START DATE	
Muscle Weakness	Hyaloronic Acid	07/01/2019	50 mg-1 capsule daily
Digestive Aid	Bacillus coagulans	10/4/2022	take one gummy bear daily after dinner
Back Pain	Pantothenic acid	09/1/202	500 mg 1 capsule daily
	Pantethine	09/01/2022	450 mg 1 capsule daily

Purpose of Safe Health Report

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