# Influence of Chronic Intake of New Sweetener Fructooligosaccharide (Neosugar) on Growth and Gastrointestinal Function of the Rat

Takahisa TOKUNAGA, Tsuneyuki OKU
and Norimasa HOSOYA[1]

*Department of Nutrition, Faculty of Medicine,
The University of Tokyo, Hongo, Bunkyo-ku,
Tokyo 113, Japan*

*Summary*    The influence of the chronic intake of a newly developed sweetener named "Neosugar" (fructooligosaccharide) on body weight gain, organ weight, serum lipids, fecal excretion and intestinal function was investigated in rats. The following results were obtained.   1) Body weight gain was diminished more severely in rats fed on 20% Neosugar diet than in rats fed on 10% Neosugar diet.   2) The wet weights of cecum and colon were greatly increased by Neosugar feeding.   3) Fecal wet weight was significantly increased and gastrointestinal transit time was shortened by Neosugar feeding compared with those of the control group.   4) Serum triacylglycerol levels were significantly lower in rats fed Neosugar, whereas serum cholesterol levels were similar to those of the control group.   5) Fecal excretions of neutral sterol and volatile fatty acids were significantly increased by Neosugar feeding. These results were quite similar, with the exception of diarrhea to those obtained using a dietary fiber such as glucomannan. Therefore, Neosugar with a pleasant-tasting sweetness appears to be an unavailable oligosaccharide with a dietary-fiber-like action.
*Key Words*   Neosugar, fructooligosaccharide, dietary fiber, chronic intake, sweetener, undigestibility, gastrointestinal

A dietary preference for sweet foods accompanied by an excessive intake of energy leads inevitably to obesity in people who continue to consume more energy than they burn. In this sense, pleasant-tasting, non-energy sweetener that is entirely safe would make it possible to enjoy sweetened food and at the same time, to avoid both obesity and its complications such as diabetes mellitus. The newly developed

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[1] 徳永隆久, 奥 恒行, 細谷憲政

$$1^F \ (1-\beta-\text{fructofuranosyl})_{n-1}-\text{sucrose}$$
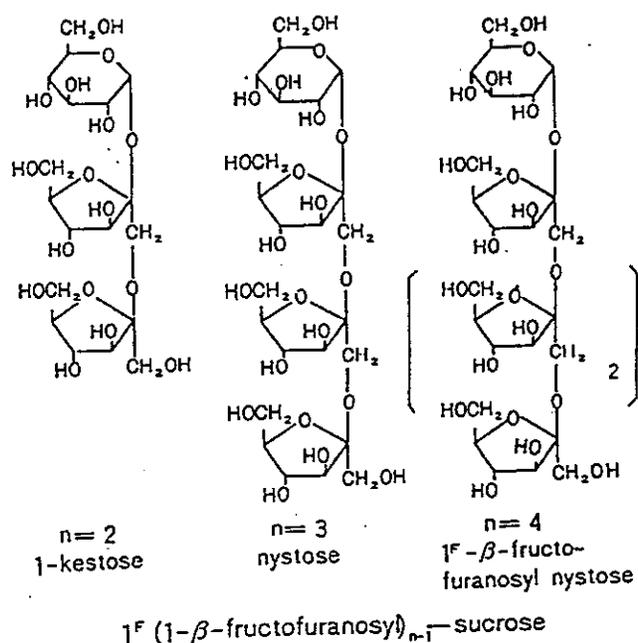
Fig. 1. Structure of fructooligosaccharides (Neosugar).

sweetener "Neosugar" may solve the universal dilemma of a dietary preference for sweet foods. Neosugar is a mixture of fructooligosaccharides such as 1-kestose ($GF_2$), nystose ($GF_3$) and $1^F$-$\beta$-fructofuranosyl nystose ($GF_4$). Its formula is given in Fig. 1. The sugar composition of Neosugar is approximately 28% $GF_2$, 60% $GF_3$ and 12% $GF_4$. The intensity of sweetness of Neosugar is about 0.4- to 0.6-fold that of sucrose, but other characteristics are similar (1–3). Fructooligosaccharides such as $GF_2$, $GF_3$ and $GF_4$ occur naturally in many kinds of plants such as the onion, asparagus root, tubers of the Jerusalem artichoke and wheat (3). At present, Neosugar can be manufactured from sucrose by a fungal fructosyltransferase (1,2).

Neosugar is not hydrolyzed by digestive enzymes in the intestinal mucosa, pancreas and internal organs (4). This observation suggests that Neosugar might not be utilized as an energy source in the body. It seems to be a pleasant-tasting non-nutritive sweetener. However, the effect of a chronic intake of Neosugar on humans and animals has not been tested previously. The purpose of the present study is to investigate the influence of a chronic intake of Neosugar on body weight gain, serum lipid levels, fecal excretion and gastrointestinal function in rats.

## METHODS

1. *Animals and diets.* Male Wistar rats (Nisseizai Co., Tokyo), initially weighing 40 to 50 g each, were fed on one of the diets shown in Table 1 *ad libitum* for 6 to 8 weeks. The only variable in the experimental diets was the carbohydrate

(%)

Table 1. Composition of diets.

| Components | Diets | | | |
|---|---|---|---|---|
| | Control | 10% Neosugar | 20% Neosugar | 20% Glucomannan |
| Corn starch[a] | 67 | 57 | 47 | 47 |
| Neosugar[b] | 0 | 10 | 20 | 0 |
| Glucomannan[c] | 0 | 0 | 0 | 20 |
| Milk casein[d] | 21 | 21 | 21 | 21 |
| Corn oil[e] | 7 | 7 | 7 | 7 |
| Salt mixture[f] | 4 | 4 | 4 | 4 |
| Vitamin mixture[g] | 1 | 1 | 1 | 1 |

[a,d,e] Clea Japan Inc., Tokyo. [b] Meiji Seika Kaisha Ltd., Tokyo, composed of $GF_2$ 28%, $GF_3$ 60% and $GF_4$ 12%. [c] Shimizu Chemical Co., Hiroshima, Japan, Tubers of Amorphophallus Konjak C. Koch. [f] Clea Japan mixture (mg/100 g diet): $CaCO_3$, 1,355; $KH_2PO_4$, 1,730; $CaHPO_4 \cdot 2H_2O$, 1,500; $MgSO_4 \cdot 7H_2O$, 800; NaCl, 600; $FeC_6H_5O_7 \cdot XH_2O$, 190; $5ZnO \cdot 2CO_2 \cdot 4H_2O$, 6; $CuSO_4 \cdot 5H_2O$, 1.26; $CoCl_2 \cdot 6H_2O$, 0.4; $Ca(IO_3)_2$, 1.54; $MnSO_4 \cdot 4H_2O$, 15.4. [g] AIN-76 mixture (mg/kg diet): thiamin·HCl, 6.0; riboflavin, 6.0; pyridoxine·HCl, 7.0; niacin, 30; calcium pantothenate, 16; folic acid, 2.0; biotin, 0.2; vitamin $B_{12}$ (0.1% trituration in mannitol), 10; vitamin A palmitate, 4,000 IU/kg diet; α-tocopherol 50 IU/kg diet; vitamin $D_3$, 1,000 IU/kg diet; menadione sodium bisulfite complex, 1.5; choline chloride, 1,000.

source. The composition of Neosugar obtained from Meiji Seika Kaisha Ltd. (Tokyo) was 28% $GF_2$, 60% $GF_3$ and 12% $GF_4$. Six rats were randomly assigned one of 4 different diets and housed in a stainless-steel, wire-bottomed cage at $25 \pm 3°C$. Body weight was recorded weekly. Eighteen hours before being killed, rats were starved and water only was supplied.

2. *Food intake, feces collection and gastrointestinal transit time.* One week before being killed, the animals were kept individually in stainless-steel metabolic cages and acclimatized to a new cage for 2 days. The daily food intake was then measured for 3 days. During this period the feces were collected to measure the daily excretion of neutral and acidic sterols and volatile fatty acids. On the following days, gastrointestinal transit time was measured using each experimental diet with 0.5% (wt/wt) of carmine red added as a marker. The period from the initial intake of the diet containing carmine red to the first excretion of feces with marker was taken as the gastrointestinal transit time.

3. *Tissue weight and serum cholesterol and triacylglycerol levels.* After measuring the transit time, the rats were starved for 18 h and killed by decapitation. Immediately after being killed, the abdominal cavity was opened and the liver, kidney, small intestine, cecum and colon were removed, cleaned and weighed.

Blood was collected when the rats were killed and the sera were prepared by centrifugation to measure cholesterol and triacylglycerol concentrations. Total cholesterol was determined using the Wako Cholesterol B-Test kit (Wako Pure Chemical Co., Tokyo), utilizing the reaction of o-phthalaldehyde(5). Triacylglycerol was measured using the Wako Triacylglycerol Test kit (Wako Pure Chemical Co.), based on the reaction of formaldehyde and acetylacetone after oxidation by sodium metaperiodate(6).

4. *Fecal sterols.* Fecal neutral and acidic sterols were determined from a pooled sample (3 days/rat) during the last week of the study. One gram of wet feces was extracted with 10 ml of acetone: ethanol (1 : 1, vol/vol) mixture. After drying the extract, 3 ml of diethyl ether and 3 ml of 1 N NaOH solution were added to separate neutral sterol and acidic sterol. The ether phase containing neutral sterol was dried and dissolved in 3 ml of acetic acid. This solution was measured by the method of Zak(7) with cholesterol as the standard. The NaOH solution phase containing acidic sterols was also measured by the method of Zak, with cholic acid as the standard. The slope of the calibration curve using cholic acid as the standard was very low compared with that of cholesterol, but was linear.

5. *Fecal volatile fatty acids.* One-half gram of collected feces was homogenized in 5 ml of 0.9% NaCl solution and centrifuged for 15 min at $11,000 \times g$. After addition of 0.1 ml of 25 mM isocaproic acid as an internal standard, 1 ml of the supernatant was extracted twice with 3 ml of diethyl ether. The diethyl ether phase was dried in the presence of 0.012 ml of 10 N NaOH solution, and resuspended in 0.3 ml of 25% formic acid. In this method, lactic acid is not involved in the diethyl ether phase. Volatile fatty acids in the extraction phase were assayed by gas chromatography (Shimadzu GC-6A, FID, Tokyo) using a Gaskuropack 54 column(8).

The data were statistically evaluated by means of Student's $t$ test.


RESULTS


1. *Body weight gain and food intake*

After feeding rats on diets containing Neosugar at 10% or 20% for 6 weeks, the body weight gain of the group receiving the 20% Neosugar diet was significantly lower compared to that of the control group ($p < 0.01$). However, in animals on the 10% Neosugar diet, no significant decrease in body weight gain was observed (Fig. 2). A remarkable suppression of body weight gain was also observed in animals consuming a diet containing 20% glucomannan, which is a kind of dietary fiber(9–11), but this was not significant when compared with that of the group receiving the 20% Neosugar diet.

Daily food intake was similar in all four groups, with the Neosugar- and glucomannan-fed rats having a slightly lower food intake (Table 2).
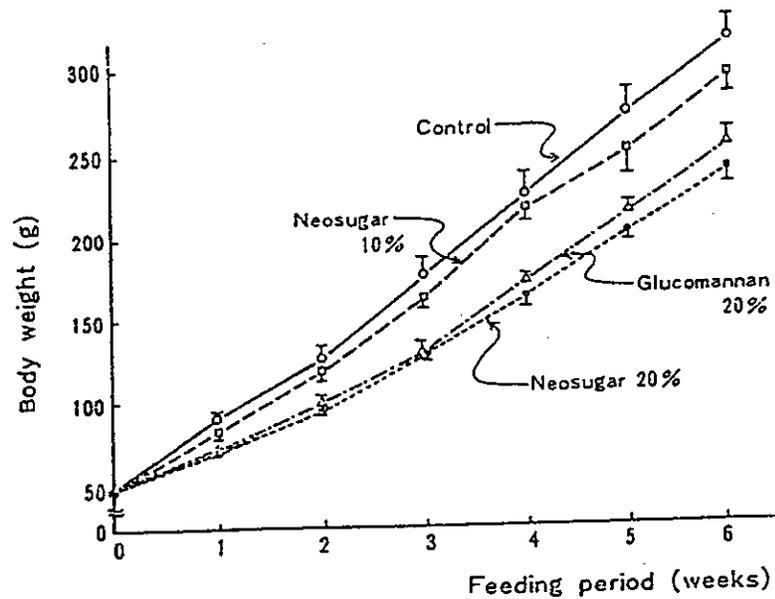
Fig. 2.   Body weight gain of rats fed on a diet containing Neosugar or glucomannan. Male Wistar rats, initially weighing 40–50 g each, were fed on a diet containing 10% or 20% of Neosugar or glucomannan for 6 weeks. Six rats in each group were kept in a cage at room temperature ($25 \pm 3°C$). Food and water were given *ad libitum*. Each bar represents the mean and standard error for each period.

Table 2.   Effect of the chronic intake of Neosugar on fecal weight and gastrointestinal transit time in rats.
Animals are the same as described in Fig. 1. Food intake and fecal weight are averaged for the three-day period at the beginning of the sixth week.   Transit time was determined using carmine red as marker as described in Methods. Each value represents the mean ± SEM.

| Groups | Food intake (g/day) | Fecal weight (g/day) | Transit time (h) |
|---|---|---|---|
| Control | $16.78 \pm 0.86$ | $0.58 \pm 0.05$ | $27.7 \pm 3.4$ |
| 10% Neosugar | $16.74 \pm 0.96$ | $0.83 \pm 0.05$** | $20.5 \pm 8.2$ |
| 20% Neosugar | $15.59 \pm 1.00$ | $1.15 \pm 0.22$** | $14.0 \pm 6.7$** |
| Glucomannan | $15.52 \pm 1.17$ | $1.77 \pm 0.25$** | $9.2 \pm 0.9$** |

** Significantly different from the control group at $p < 0.01$.

## 2. Effect of Neosugar intake on various organ weights

The ratio of organ wet weight to body weight after feeding for 6 weeks is shown in Table 3. The feeding of 10% Neosugar diet and 20% Neosugar diet produced a significant increase in both wet weight and the ratio of cecum to colon weights

Table 3. Effect of Neosugar intake on the wet weight of various organs in rats. Animals are the same as described in Fig. 1. Immediately after decapitation, each organ was removed and cleaned, and the wet weight of the whole organ was measured. Each value represents the mean ± SEM.

| | Control | 10% Neosugar | 20% Neosugar | 20% Glucomannan |
|---|---|---|---|---|
| | | (g) | | |
| Body weight | 313.5 ± 13.0 | 291.3 ± 12.0 | 237.0 ± 8.8** | 250.8 ± 7.4** |
| | | (% of body weight) | | |
| Liver | 2.88 ± 0.05 | 2.98 ± 0.12 | 3.08 ± 0.31 | 2.97 ± 0.07 |
| Kidney | 0.36 ± 0.01 | 0.36 ± 0.02 | 0.38 ± 0.01 | 0.35 ± 0.01 |
| Small intestine | 1.85 ± 0.05 | 1.94 ± 0.15 | 2.29 ± 0.16* | 2.84 ± 0.07** |
| Cecum | 0.17 ± 0.01 | 0.37 ± 0.04** | 0.63 ± 0.05** | 0.46 ± 0.02** |
| Colon | 0.29 ± 0.01 | 0.35 ± 0.02* | 0.49 ± 0.03** | 0.35 ± 0.01* |

*,** indicate significant difference from the control group at $p < 0.05$ and $p < 0.01$, respectively.

($p < 0.01$ and $p < 0.05$, respectively). A greater effect was observed in the cecum than in the colon of animals fed on the 20% Neosugar diet. Also, feeding of the 20% Neosugar diet, but not the 10% Neosugar diet, increased significantly the wet weight of the small intestine. However, no significant increase in the weight of liver and kidney was observed. In animals fed on 20% glucomannan diet, the cecum and colon wet weights increased significantly as in the case of the 20% Neosugar diet ($p < 0.01$).

### 3. Effect of Neosugar intake on fecal weight and gastrointestinal transit time

It has been demonstrated that fecal volume and weight are increased markedly and that the gastrointestinal transit time is shortened when undigestible polysaccharides such as dietary fiber are given to rats (9,12,13). As shown in Table 2, the fecal wet weight increased significantly in animals fed on either the 10% or the 20% Neosugar diet ($p < 0.01$), although the range was considerable. The greatest effect was observed in animals fed on a 20% glucomannan diet.

The gastrointestinal transit time was about 28, 21 and 14 h in the control, 10% and 20% Neosugar groups, respectively (Table 2). That of the 20% glucomannan group was shortest among all four groups: about 9 h. Gastrointestinal transit time was in inverse correlation to the fecal wet weight.

### 4. Effect of Neosugar intake on serum cholesterol and triacylglycerol levels

The effects of dietary Neosugar on serum cholesterol and triacylglycerol levels are shown in Table 4. The serum cholesterol level was slightly but not significantly reduced by the 20% Neosugar diet. The serum triacylglycerol level was significantly

Table 4.  Effect of Neosugar intake on serum cholesterol and triacylglycerol levels. Animals are the same as described in Fig. 1. Blood collected was centrifuged to obtain serum and used to determine cholesterol and triacylglycerol as described in METHODS. Each value represents the mean ± SEM.

| | Control | 10% Neosugar | 20% Neosugar | 20% Glucomannan |
|---|---|---|---|---|
| | | (mg/100 ml of serum) | | |
| Cholesterol | 63.0 ± 3.7 | 63.4 ± 3.1 | 60.0 ± 2.1 | 59.2 ± 3.9 |
| Triacylglycerol | 209.2 ± 21.8 | 150.0 ± 4.0** | 144.6 ± 23.0* | 122.6 ± 10.4** |

*,** indicate significant difference from the control group at $p < 0.05$ and $p < 0.01$, respectively.

decreased by Neosugar intake. The effect was greater in animals fed on the 20% Neosugar diet than in those fed on the 10% Neosugar diet. A significant reduction in serum triacylglycerol levels was observed in animals receiving a 20% glucomannan diet as well as in the 20% Neosugar diet group. However, glucomannan had no effect on serum cholesterol levels.

*5. Effect of dietary Neosugar on fecal excretion of sterols and volatile fatty acids*

The fecal excretion of sterol is increased significantly by chronic intake of dietary fiber which is not hydrolyzed by digestive enzymes, through the inhibition of intestinal cholesterol and bile acid absorption (14,15). Also, the fecal excretion of volatile fatty acids is enhanced by dietary fiber intake, by altering the intestinal microflora (16,17). Since Neosugar is not hydrolyzed by digestive enzymes in intestinal mucosa (4), it appears to increase the fecal excretion of sterol and volatile fatty acids in the same way as dietary fiber.

Excretion of neutral sterols in the feces increased significantly in animals fed either Neosugar or glucomannan. Acidic sterol excretion slightly but significantly increased in animals fed on the 20% Neosugar diet. However, in animals fed on the 20% glucomannan diet, the excretion of acidic sterol increased remarkably compared to that with the 20% Neosugar diet (Fig. 3).

The concentration of volatile fatty acids per gram of wet feces greatly increased in all animals fed Neosugar or glucomannan compared with the control group (Fig. 4). In animals fed Neosugar, the greatest increase was in acetic acid and the second in propionic acid. The increase in butyric acid was the smallest observed. In animals fed glucomannan, the excretion of propionic acid showed the greatest increase among the volatile fatty acids. Only slight increases of butyric acid and valeric acid were observed. It is possible to conclude that Neosugar intake stimulates the fecal excretion of sterols and increases the fecal excretion of volatile fatty acids.
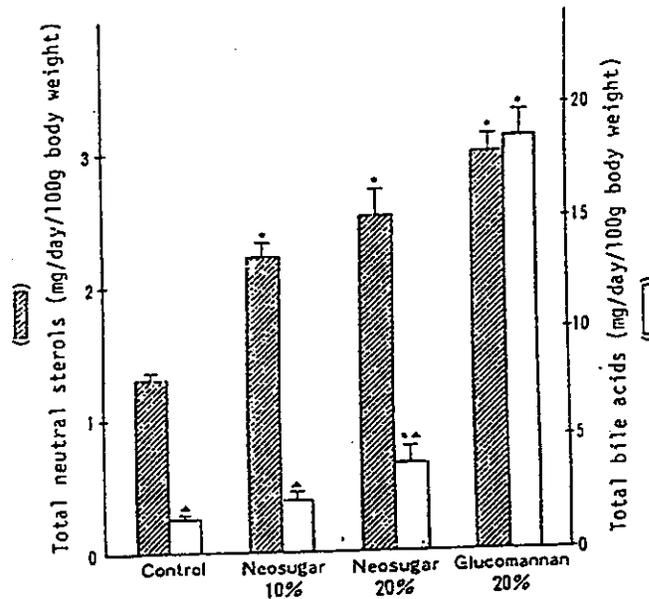
Fig. 3. Effect of Neosugar intake on the fecal excretion of neutral and acidic sterols. Six male Wistar rats, initially weighing 40–50 g each, were raised on the diet as described in Table 1 for 6 weeks. The feces collected during the sixth week were used for the measurement of sterols after extraction with an acetone: ethanol (1:1) mixture. Neutral and acidic sterols were determined by the procedures described in METHODS. * Significantly different from the control group at $p < 0.01$. ▲, significantly different from the glucomannan group at $p < 0.01$.



Concentration of VFA (mg/g of wet feces)
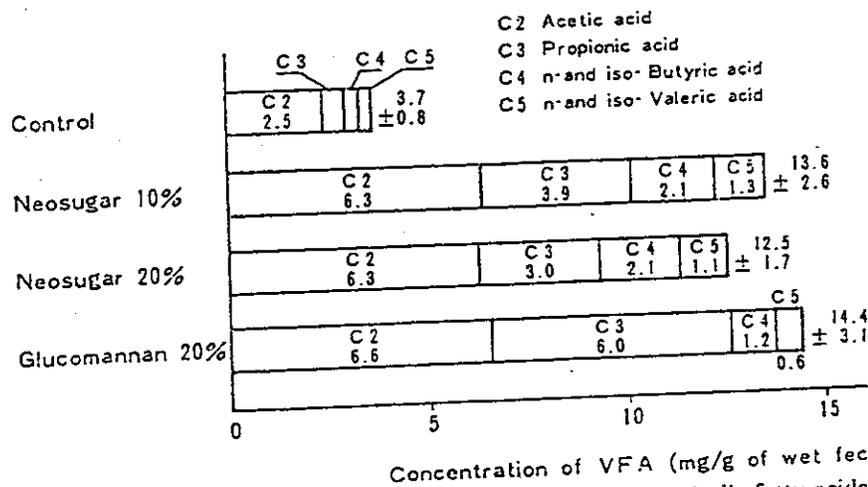
Fig. 4. Effect of Neosugar intake on the fecal excretion of volatile fatty acids in rats. The feces, which were obtained from the animals as described in Fig. 2, were used for the determination of volatile fatty acids after extraction with diethyl ether from the supernatant of fecal homogenate. Volatile fatty acids were analyzed by gas chromatography as described in METHODS. The results are expressed as the mean of 6 rats.

## DISCUSSION

Neosugar is not hydrolyzed by α-amylase and digestive enzymes in the intestinal mucosa, and the long-term feeding on Neosugar does not lead to the production of hydrolyzing enzymes in the intestine and other organs(4). In the present study, the food intake was similar for all groups. Therefore, the smaller body weight gain with Neosugar feeding suggests that Neosugar is not fully utilized as an energy source. It is possible that a portion of Neosugar taken orally is metabolized by intestinal microflora to volatile fatty acids and utilized as an energy source.

Several workers have observed colonic atrophy and reductions in epithelial cell proliferation and intestinal absorption in animals given a chemically defined or elemental diet (*18–20*). This atrophy of the intestine has been attributed to a lack of bulk in the intestinal lumen. Neosugar must have a bulking effect in the gut, because it is not hydrolyzed by digestive enzymes. Therefore, enlargement of the cecum and colon of rats given Neosugar appears to be an adaptation to the bulk content in the lumen of cecum and colon. Neosugar is thought to maintain normal epithelial cell proliferation through its bulk effect as dietary fiber. A similar enlargement of the cecum and colon has been observed in rats given dietary fibers such as pectin. glucomannan, cellulose, guar gum and wheat bran (*9,10,21–24*). Accordingly, the cecum and colon enlargement accompanying Neosugar feeding indicates that Neosugar is an undigestible and/or unabsorbable oligosaccharide and has a bulking effect in the intestinal lumen.

Rats developed diarrhea after starting Neosugar feeding. This stopped within 2 to 3 weeks, differing with individual rats. A similar phenomenon is also observed in rats given maltitol, sorbitol or xylitol which is an undigestible and/or unabsorbable sugar alcohol with a sweet taste (*25,26*). However, dietary fiber, a polysaccharide with a high molecular weight, does not produce diarrhea in rats. The diarrhea caused by ingestion of unavailable and/or unabsorbable oligosaccharides is more intense the smaller the molecular weight. Conversely, the occurrence of diarrhea with the feeding of sugars indicates generally that a sugar is undigestible and/or unabsorbable and has a small molecular weight. Therefore, diarrhea caused by Neosugar feeding yields proof that Neosugar is undigestible and/or unabsorbable. It has been demonstrated that single-dose intake of Neosugar at less than 0.8 g per kg of body weight does not produce diarrhea in males, but that it does at above this level, and that females are more resistant to diarrhea than males (*27*). Daily Neosugar intake of rats in the present study was more than 10 g per kg of body weight in the early period of feeding, and caused diarrhea. However, the diarrhea stopped within 2 to 3 weeks. Thus humans may be more sensitive to Neosugar-induced diarrhea than rats.

Fecal volume is increased markedly and the intestinal transit time is significantly shortened in animals given dietary fiber. The results of the present study indicate that Neosugar as well as dietary fiber significantly increased fecal weight

and decreased the gastrointestinal transit time. These results suggest that Neosugar has a bulking effect similar to dietary fiber, and may suppress the digestion and absorption of nutrients in the intestine.

The significant reduction of serum triacylglycerol levels by chronic intake of Neosugar is thought to be due to the suppression of the total energy intake, decreasing the energy extracted from Neosugar. Serum cholesterol levels were not decreased by Neosugar feeding, although the fecal excretion of sterol was significantly increased. This contradiction may indicate that the synthesis of cholesterol in organs such as the liver and the intestine is accelerated rather than the fecal excretion of sterols. It is well known that water-soluble dietary fibers such as glucomannan, pectin and guar gum promote the fecal excretion of sterol, inhibit absorption of sterol from the intestine, and decrease serum cholesterol levels (14,15). However, the mechanism of stimulation of the fecal excretion of sterols is unknown in animals given Neosugar.

Fecal excretion of volatile fatty acids was greatly increased in both groups fed Neosugar and glucomannan, but the amounts of volatile fatty acids were different. This result indicates that intestinal microflora differed in rats respectively fed on Neosugar and glucomannan. In fact, Neosugar stimulates the proliferation of Bifidobacterium and suppresses the growth of Escherichia and Clostridium (3).

Although Neosugar is a water-soluble oligosaccharide greatly different from high molecular weight dietary fibers, it produced several similar physiological actions. Neosugar thus has the benefits of a low-energy sweetener with effects similar to those of dietary fiber.

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