in one possibly important matter in that they represented the feeding of single small doses of tagged iron; whereas, the work done on dogs by the other investigators represented daily feedings of iron and liver extract over several weeks periods. Recently Granick[5] has shown that the ferritin of the gastro-intestinal tract increases following the feeding of iron. Thus we must keep in mind the possibility that the body may adapt itself to the absorption of larger amounts of iron through some as yet unknown mechanism for the production of the material which itself is probably concerned with iron absorption.

It is important also to keep in mind the fact that the experimental standard anemic dogs used by Whipple and Robscheit-Robbins in their classical experiments on factors involved in hemoglobin regeneration are not simple "iron deficiency" experimental animals. The iron content of the salmon-bread diet fed these animals is adequate for normal growth and maintenance, but probably not sufficient to provide for the increased demands imposed by the necessity of removal of large amounts of blood occasioned by feedings of active supplements. Since it has been shown, as mentioned earlier,[1] that under certain circumstances restriction of proteins may cause a lowered ability to form sufficient hemoglobin in experimental hemorrhagic anemia in dogs, it is possible that under the conditions of the experiments cited by Whipple, Robscheit-Robbins, and Walden that there was a more complicated deficiency involved, in which more than one factor or two interrelating factors were involved.

Whatever the explanation may be as to the different results obtained under these widely various sets of conditions, it is apparent that any influence on hematopoiesis exerted by liver extract No. 55 is not one which acts through its ability to augment the absorption of the iron from the gastro-intestinal tract.

*Summary.* Iron tagged with the radioactive isotope $Fe^{59}$ was fed with and without supplements of liver extract No. 55 to a group of 11 normal adult women. There were no obvious differences in the absorption and utilization of iron when this material was given alone or in conjunction with the "secondary anemia fraction of liver." In one case of human iron deficiency due to multiple acute and chronic hemorrhage there was also no difference in the absorption of iron as indicated by this method.

The "summation response" described by Whipple, Robscheit-Robbins and Walden is apparently not related to the effect of the secondary liver extract on *absorption of iron* in the gastro-intestinal tract.

5 Granick, S., *J. Biol. Chem.*, 1946, **164**, 737.

## 16025

# The Influence of Oral Saccharin on Blood Sugar.

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The purpose of this investigation was to determine whether or not sweet taste as a nervous sensation has an effect on carbohydrate metabolism. It was found that saccharin, a substance of intensely sweet taste, can cause a decrease in blood sugar, presumably through the reflex liberation of insulin.

*Methods.* Saccharin (Sodium salt o-benzoic-acid-sulfimide) was given to human subjects in doses of 0.05 g in 80 ml water. In one group of experiments the effect of single doses, and in another group the effect of repeated doses of saccharin solution was followed.

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TABLE I

Blood sugar values, determined at 10 minute intervals in individuals under normal fasting condition (F) and in the same individuals under the same conditions after oral administration of 0.05 gm saccharin in 80 ml water (S). Blood sugar values are expressed in terms of percentage of the blood sugar level at 0 time.

| Indiv. Subj. No. | 10 min | | 20 min | | 30 min | | 40 min | | 50 min | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F | S | F | S | F | S | F | S | F | S |
| 1. | 96.2 | 98.4 | 104.2 | 90.0 | 98.1 | 84.3 | 102.1 | 93.4 | 98.8 | 90.1 |
| 2. | 98.1 | 100.1 | 102.4 | 91.4 | 97.3 | 85.2 | 96.4 | 87.6 | 96.2 | 98.3 |
| 3. | 97.0 | 96.2 | 100.1 | 93.2 | 96.4 | 88.7 | 100.1 | 88.2 | 103.2 | 104.1 |
| 4. | 96.6 | 98.8 | 98.4 | 85.1 | 101.1 | 90.3 | 95.4 | 95.1 | 99.3 | 99.1 |
| 5. | 101.4 | 99.3 | 97.3 | 80.3 | 95.2 | 80.2 | 98.3 | 85.3 | 100.1 | 97.5 |
| 6. | 97.6 | 102.4 | 96.4 | 90.1 | 93.4 | 78.1 | 97.6 | 81.1 | 98.8 | 93.6 |
| 7. | 104.2 | 101.3 | 101.3 | 83.1 | 95.3 | 84.1 | 99.4 | 92.1 | 92.3 | 97.2 |
| 8. | 98.9 | 97.7 | 100.2 | 92.2 | 96.0 | 85.3 | 96.2 | 98.6 | 100.0 | 106.9 |
| 9. | 100.1 | 99.8 | 97.0 | 95.4 | 97.1 | 82.0 | 97.0 | 99.1 | 95.4 | 94.2 |
| | M=98.8 | M=99.3 | M=99.6 | M=88.8 | M=96.6 | M=84.2 | M=98.0 | M=91.2 | M=98.2 | M=97.9 |
| | t = 0.5 | | t = 5.7 | | t = 7.7 | | t = 3.2 | | t = 0.15 | |

In the first group 9 persons were used. In the morning, before eating, the subjects remained in bed, and blood sugar determinations were carried out at 10 minute intervals for 50 minutes. Blood was taken from the cubital vein and blood sugar determinations were done with 0.1 ml samples by an iodometric titration method.[1] A fasting level was thus established. Each subject was then used at the same time the next day under the same conditions for the saccharin experiment. Ten minutes after the first blood sample was taken, the subject drank a solution of saccharin (0.05 g dissolved in 80 ml of water). As standard procedure the drinking lasted for 5 minutes.

*Results.* In 5 control experiments 80 ml water had no significant effect on the blood sugar. The results are given in tables where the blood sugar values are expressed in terms of per cent of the initial blood sugar level. This initial level was arbitrarily taken as 100. In Table I are shown the changes in blood sugar level following a single saccharin administration. The means of 9 parallel experiments were compared with the means of 9 controls. The significance of the difference between the means was tested by calculating the "t" values according to Fisher.[2] Following administration of the saccharin solution a rapid decrease in blood sugar occurred which ended after 30 minutes.

The second group of 6 persons was given the same amount of saccharin solution as was given to Group I, but it was divided into 4 parts which were drunk at 10 minute intervals. Blood samples were drawn at 15 minute intervals for 90 minutes. The administration of saccharin solution in 4 parts resulted in the same drop in blood sugar, except that the hypoglycemia lasted 75 minutes. The results of this experiment are shown in Table II.

*Discussion.* A comparison of the 2 series of experiments reveals no quantitative correlation between the decrease in blood sugar and the amount of saccharin taken. Salkowski,[3] and Carlson, Eldridge and Foran[4] showed that saccharin has no pharmacological activity in the small doses used here. In both experiments, the sensation of intense sweet taste was produced and there is good reason to believe that this taste, and not the amount of saccharin was responsible for the blood sugar effect. It would be of interest to test other sweet tasting substances for this effect. Syllaba[5] reported an increase in blood sugar after the administration of saccharin by means of a gastric tube in rabbits and man. He suggested that this effect is due to a reflex mechanism between the intestinal wall

1 Fujita, A., and Iwatake, D., *Biochem. Z.*, 1931, **242**, 43.

2 Fisher, R. A., *Statistical Methods for Research Workers*, 1930, Oliver and Boyd, London.

3 Salkowski, A., *Virchows Arch.*, 1886, **105**, 46.

4 Carlson, J., Eldridge, and Foran, *J. Metabol. Res.*, 1929, **3**, 451.

5 Syllaba, G., *Am. J. Physiol.*, 1929, **90**, 535.

TABLE II

Blood sugar values determined at 15 minute intervals in individuals under normal fasting conditions (F) and in the same individuals under the same conditions after oral administration of 0.05 gm saccharin in 80 ml water, given in 4 equally divided doses at 10 minute intervals after 0 time. Blood sugar values are expressed in the same way as in Table I.

| Indiv. Subj. No. | 15 min | | 30 min | | 45 min | | 60 min | | 75 min | | 90 min | | 105 min | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F | S | F | S | F | S | F | S | F | S | F | S | F | S |
| 1. | 98.0 | 100.0 | 101.2 | 87.2 | 100.0 | 81.2 | 96.2 | 91.0 | 95.4 | 93.6 | 99.3 | 106.1 | 98.3 | 104.2 |
| 2. | 96.0 | 86.0 | 104.4 | 84.3 | 96.2 | 84.0 | 95.3 | 90.2 | 98.0 | 85.4 | 105.3 | 97.6 | 105.1 | 102.1 |
| 3. | 101.0 | 88.0 | 96.0 | 86.2 | 98.5 | 85.7 | 101.0 | 81.6 | 96.2 | 90.0 | 103.7 | 92.1 | 102.0 | 106.1 |
| 4. | 97.0 | 97.1 | 100.0 | 89.2 | 102.2 | 82.0 | 103.0 | 83.7 | 101.0 | 87.3 | 96.7 | 106.0 | 100.1 | 104.2 |
| 5. | 98.0 | 90.7 | 97.4 | 87.0 | 97.1 | 86.3 | 102.7 | 80.0 | 97.3 | 91.1 | 102.0 | 95.5 | 97.3 | 97.3 |
| 6. | 99.2 | 90.6 | 98.8 | 84.0 | 99.0 | 82.5 | 100.4 | 85.3 | 98.0 | 88.3 | 104.1 | 106.1 | 99.3 | 96.2 |
| | M= 98.3 | M= 91.0 | M= 99.6 | M= 86.3 | M= 98.8 | M= 83.5 | M= 99.6 | M= 84.0 | M= 97.7 | M= 89.2 | M= 101.8 | M= 100.5 | M= 100.3 | M= 100.1 |
| | t = 5.6 | | t = 7.7 | | t = 10.4 | | t = 6.5 | | t = 6.0 | | t = 0.4 | | t = 0.1 | |

and the liver. Althausen and Wewer[6] could not confirm this observation. These authors disregarded the relatively small but reproducible decrease in blood sugar after saccharin consumption, although according to their results this decrease was observed. Fischer and Schroter[7] investigated the effect of saccharin on human patients suffering from various diseases, but no control tests on healthy subjects were carried out. Some of these patients showed a decrease in blood sugar, but the authors attached no significance to this phenomenon. The small but significant decrease in blood sugar level can be seen only under circumstances in which all other influences are eliminated or controlled in every way possible. As an explanation of the observed phenomenon, it seems logical to think of insulin liberation, called forth by a nervous impulse through the sensory fibers from the taste endplates to the vagus centers. Since Geiger's experiments[8] showed that the vagus is a secretory nerve of the islets of Langerhans, it is possible that the efferent part of this reflex arc is in the vagus. Other afferent stimuli from sensory organs, such as the olfactory, cause a similar decrease in blood sugar, as reported by Bassi and Pascucci,[9] whose observation also strengthens the possibility of the existence of the above described reflex mechanism.

*Summary.* 1. Oral administration of an aqueous solution containing 0.05 g of saccharin caused a decrease of 12 to 16% in the blood sugar level of normal individuals. Water alone had no significant influence.

2. The decrease of blood sugar was not proportional to the saccharin dosage.

3. Administration of the saccharin in 4 portions during a 40 minute period increased the duration of hypoglycemia.

4. It is suggested that this phenomenon is due to the influence of the sweet taste, which may act by means of a reflex mechanism to induce insulin secretion.

6 Althausen, T. L., and Wewer, G. K., PROC. SOC. EXP. BIOL. AND MED., 1937, **35**, 517.

7 Fischer, F., and Schroter, A., *Dtsch. Med. Wschr.*, 1935, **61**, 1354.

8 Geiger, E., *Arch. Exp. Path. and Pharmacol.*, 1928, **134**, 317.

9 Bassi, M., and Pascucci, P., *Rass. Neur. Veget.*, 1943, **3**, 68.