CXXVIII. AN INVESTIGATION OF QUEBRACHITOL AS A SWEETENING AGENT FOR DIABETICS.

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QUEBRACHITOL (*l*-methylinositol) was first isolated by Tanret [1887] from quebracho bark. The latex of rubber trees contains about 2 %, and it was first obtained from this source by de Jong [1906], and has recently been prepared on a much larger scale by Rhodes and Wiltshire [1932]. The present study has been carried out at the instigation of the Rubber Research Association, to whom we are indebted for the supply of quebrachitol. No physiological experiments seem to have been carried out with quebrachitol, but the less soluble non-methylated *l*-inositol which is widespread in nature has been extensively studied, and the results fully reviewed by Needham [1926].

The quebrachitol which was supplied to us was an almost white crystalline powder. It dissolved readily in water in much the same way as glucose, but always left an amorphous brown residue, which looked a little like ferric hydr-oxide. This was filtered off before use. The chemical estimation of quebrachitol is difficult, and this was not undertaken in the blood, urine or intestinal residues, as this seemed unnecessary for the investigation in hand.

To be a suitable sugar substitute for diabetics any material must satisfy three requirements.

(1) It must have a pleasant sweet taste in relatively low concentration. If the substance has a high degree of solubility and will make a sweet syrup for cooking, so much the better.

(2) It must not be metabolised as a sugar.

(3) It must be free from harmful effects even in large doses.

This last consideration is important, for the whole value of such a substitute is lost if it can only be taken in measured doses. The use of drugs to counteract any harmful effects is, of course, not to be considered. Quebrachitol has therefore been tested on these three points.

1. *Taste.* Quebrachitol has a sweet taste. In the opinion of a number of independent persons it was not nearly so sweet as glucose, which itself was not so sweet as cane-sugar. Some stated that quebrachitol had a metallic taste. Two kinds of fruit were cooked with quebrachitol. $\frac{1}{4}$ lb. blackberries (120 g.) were stewed with (a) 7 g. quebrachitol, (b) 28 g. quebrachitol, (c) 14 g. cane-sugar, and (d) with no additions. Five people tasted these independently. All agreed that the blackberries stewed with cane-sugar were the sweetest. Only one person could detect any sweetening effect from the 7 g. of quebrachitol. All but one thought that 28 g. of quebrachitol made the fruit pleasantly sweet and as palatable, or nearly so, as the cane-sugar. One person stated that the quebrachitol merely conferred an unpleasant metallic taste, and preferred to have no sweetening rather than quebrachitol. In the second place $\frac{1}{2}$ lb. (227 g.) of

stewing gooseberries were cooked with (a) 14 g. of quebrachitol, (b) 28 g. of quebrachitol, (c) 42 g. of quebrachitol, and (d) with no additions. The general opinion among the tasters was that 14 g. of quebrachitol was quite inadequate and that 28 g. or 42 g. were required to make the gooseberries palatable. The same person who had preferred blackberries with no additions to those with quebrachitol confirmed this opinion with the gooseberries.

Quebrachitol, therefore, from these limited gustatory tests, appears to be a satisfactory sweetening agent for most palates, provided relatively large amounts are used.

2. *The effect of quebrachitol on sugar metabolism* has been tested as follows:

(a) The blood-sugar curves of one normal person and two mild diabetics have been studied after 50 g. quebrachitol had been taken by mouth and these compared with the blood-sugar curves after similar amounts of carbohydrate as glucose or bread. The test was made in all cases after an overnight fast.

The results are collected in Table I and it will be seen that quebrachitol does not raise the reducing substances (Folin-Wu estimation) in the blood of a normal person. In the two diabetics small rises were observed but they were

Table I.

Name and classification	Substance and dose	Times and administration and blood-sugar values (%)				
		0	$\frac{1}{2}$ hour	1 hour	$1\frac{1}{2}$ hours	2 hours
Mr D. (normal)	50 g. glucose	0.093	0.138	0.098	0.117	0.087
	50 g. quebrachitol	0.115	0.104	0.100	0.109	0.115
Mr O. (mild diabetic)	45 g. glucose (as bread)	0.100	0.181	0.266	—	0.186
	50 g. quebrachitol	0.113	0.136	0.142	0.148	0.152
Mrs P. (mild diabetic)	50 g. glucose	0.146	0.222	0.278	0.263	0.217
	50 g. quebrachitol	0.125	0.127	0.140	0.148	0.146

so slight in comparison with those after glucose that they were of doubtful significance. Small rises similar to this have been obtained after "sionon" (*d*-sorbitol).

(b) Two diabetics on insulin voluntarily took an overdose in the morning, and when symptoms of hypoglycaemia began drank a solution of 20 g. of quebrachitol in water. In both cases the symptoms persisted for half an hour, after which 20 g. glucose by mouth rapidly removed the hypoglycaemia. The details of the blood-sugars are given in Table II. It is evident that quebrachitol by mouth did not relieve hypoglycaemia.

Table II.

Name	Blood-sugar (%)			
	At commencement of overdose before taking quebrachitol	$\frac{1}{2}$ hour after taking quebrachitol: before taking glucose	15 mins. after taking glucose	$\frac{1}{2}$ hour after taking glucose
R. D. L.	0.052	0.050	0.072	0.107
H. R. M.	0.066	0.067	0.091	—

(c) A series of rats (Wistar strain, from the Glaxo laboratories, weight 150 to 220 g.) were given glucose, quebrachitol or water by stomach tube, and killed 3 hours later under urethane anaesthesia. Portions of liver were removed and

estimated for glycogen by a micro-Pflüger method [Lawrence and McCance, 1931]. The results (Table III) show that the liver contained no more glycogen after quebrachitol than it did after water, and that quebrachitol given by mouth had no glycogenetic action. The storage of glycogen after glucose served to show that the technique was satisfactory.

Table III.

Liver-glycogen (%)		
3 hours after quebrachitol	After tap-water	3 hours after glucose
0.122	0.196	1.150
0.188	0.314	0.877
0.231	0.086	0.456
0.162	0.109	0.518
0.075	0.126	1.020
0.110	0.119	1.840
0.080	—	—
Mean 0.130	0.160	0.980

2 rats received 2 g. of quebrachitol and 2 received 2 g. glucose; the remainder received 1.2 g. of glucose or quebrachitol.

So far, therefore, as can be judged from these experiments, quebrachitol does not act as a sugar in metabolism. This is in keeping with the results obtained with inositol, for the latter has been shown (*a*) not to lead to glycogen deposition in the liver [v. Mehring, 1877; Mayer, 1907], (*b*) not to lead to lactic acid formation [Embden and Griesbach, 1914; Griesbach and Oppenheimer, 1913; Oppenheimer, 1912], (*c*) not to raise the R.Q. [Anderson, 1916].

3. *Harmful effects.* Unfortunately these are very obvious. All three persons who took 50 g. of quebrachitol by mouth had fairly severe diarrhoea, passing 2 to 5 very watery motions between 1 and 3 hours afterwards. Of the two persons who took 20 g. to test the effect on hypoglycaemia, one suffered merely from slight colic about 2 hours later, but the other had very severe diarrhoea about an hour later, and recurrent colic for 30 hours. When 1 to 2 g. was administered to the rats during the glycogen experiments, the whole of the intestines, and particularly the small intestine, was observed to be distended with fluid and extremely hyperaemic. It is probable that little or none of the quebrachitol had been absorbed. Sections of the gut were cut from two of these rats, and also from two controls to which glucose had been given. Dr Creed has very kindly examined these sections and has reported that the intestines of the animals receiving quebrachitol were very hyperaemic, but that there was no evidence of shedding of the epithelium or infiltration with inflammatory cells.

These effects are similar to those obtained with inositol. Anderson [1916], for example, found that only a small percentage of the amount administered by mouth could be recovered from the urine, whereas 50 % appeared in the urine after injection. Both Anderson [1916] and Anderson and Bosworth [1916] noted diarrhoea after inositol, but Anderson and Bosworth stated that in man this passed off after a few days. Inositol has been shown by perfusion experiments to increase the force of the heart-beat and ultimately stop the heart in systole [Brissemoret and Chevalier, 1908; Hewitt and Da Souza, 1920-21; Sachs, 1906]. No action on the heart has been reported when inositol has been taken by mouth and this has been our experience with quebrachitol.

SUMMARY.

1. Quebrachitol, which chemically resembles inositol, has similar physiological effects.
2. When taken by mouth it does not relieve hypoglycaemia, raise the blood-sugar or lead to the deposition of glycogen in the liver:
3. It is not nearly so sweet to the taste as cane-sugar, and two or three times the amount is necessary to obtain the same effect on the palate.
4. In such amounts it has produced either colic or diarrhoea.
5. Its use as a sweetening agent is not to be recommended.

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