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Methyl Cellulose as a Colloid Laxative.

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Because of the shortage of vegetable gums, materials which can be more readily obtained are needed to replace them. One of the most interesting new products is methyl cellulose, which is manufactured by forming methyl ethers from purified cellulose with caustic soda and methyl chloride. This is a white product resembling cotton, which dissolves readily in cold water, forming stable colloidal solutions, which are neutral, not hydrolyzed by acids or alkali, and not subject to growth of molds. The viscosity of the solution depends on the degree of degradation of the cellulose molecule, and products are available commercially having viscosities ranging between 15 and 4000 centipoises in 2% solution.* The material flocculates out of aqueous solution when heated, but readily redissolves as it cools. In fact, a quick way to make a solution is to boil with water, and then cool in a refrigerator.

Thus far adequate pharmacologic studies of this compound have not been published. Kehoe found[1] that injection or ingestion of large amounts in white rats for as long as 6 months caused no detectable pathological changes. Hueper injected large volumes of methyl cellulose solutions in dogs and rabbits, producing effects resembling those of acacia and related colloidal materials which cannot be metabolized by the cells.[2] He also reported on its use intravenously in experimental shock.[3] Clemens and Read[4] have described its use as an emulsifier or binder in pharmaceutical and cosmetic preparations, and it is believed to be fairly widely used for such purposes at present in this country. The present observations deal with its suitability for use as a colloidal laxative similar to gum karaya and psyllium seed products.[5]

Five grams of methyl cellulose swell in a 500 cc graduate of distilled water to about 200 cc, the final volume depending on the fineness of the powder, thoroughness of wetting, etc. If complete wetting occurs, the compound disperses completely giving a thick solution or gel, the viscosity of which depends on the concentration and grade of the methyl cellulose. Swelling is not materially modified by concentrations of hydrochloric acid, sodium bicarbonate, or sodium chloride, such as it might come in contact with in the body.

Effects on Growth of Rats. To test the possible toxic effects of prolonged ingestion of the compound, 10 male and 10 female rats were used. The animals were fed Tioga meal, to which was added 10% methyl cellulose (Methocel (Dow) 4000 c.p.s.) to the food of one-half of them. In Table I are summarized the results of observations for 95 days. The male rats on methyl cellulose gained the same as the controls, and consumed the same average weight of food. In as much as the energy content of the methyl cellulose containing food was 10% less than that of the control, there must have been unrecognized inaccuracies in weighing the food eaten, possibly through scattering, or changes in the energy levels of the animals, to account for the discrepancy between food intake and growth.

The female rats on methyl cellulose gained an average of 107.3 g as compared to 125.0 g

* Methocel (Dow Chemical Company) and Methyl Cellulose (Hercules Powder Company).

1 Kehoe, R. A., personal communication.

2 Hueper, W. C., *Arch. Path.*, 1942, **33**, 1.

3 Hueper, W. C., Martin, G. J., and Thompson, M. R., *Am. J. Surg.*, 1942, **56**, 629.

4 Clemens, H., and Reed, H. W., *Australasian J. Pharm.*, 1939, **20**, 191 (Abstracted in *J. Am. Pharm. Assn., Pharm. Abst. Section*, 1940, **6**, 25).

5 Gray, H., and Tainter, M. L., *Am. J. Digest. Diseases*, 1941, **8**, 130.

TABLE I.
Effects of Ingestion of Methyl Cellulose (10%) in the Food for 95 Days on 20 White Rats.

Group	Avg body wt, g		Avg food intake, g a day	Avg organ wt as % of body wt				
	Initial	Final		Heart	Liver	Spleen	Kidney	Stomach
Male Controls	49.6	228.5	15.0	0.42	5.04	0.33	1.08	0.60
Male—Methyl Cellulose	51.0	230.4	15.1	0.41	4.74	0.42	1.06	0.67
Female Controls	45.6	170.6	13.9	0.40	5.00	0.49	1.11	0.76
Female—Methyl Cellulose	45.0	152.3	12.2	0.41	5.10	0.41	1.07	0.89

TABLE II.
Effects of Various Preparations of Methyl Cellulose on the Stools of Human Subjects.

Preparation	Total No. of days	Avg No. of stools a day	Avg wt stools, g a day		Avg water content of stools, %
			Wet	Dry	
Control Days	80	1.09	127.4	23.9	81.2
35% methyl cellulose + 65% bran, 5 g a day	5	1.8	145.2	31.4	78.4
The same, 10 g a day	13	1.5	160.5	30.8	80.8
3.5% MgO + 35% methyl cellulose + 61.5% bran, 5 g twice a day	11	1.5	179.5	34.5	80.7
10% MgO + 45% methyl cellulose + 45% bran, 5 g twice a day	16	1.7	177.1	29.8	83.2
10% MgO + 90% methyl cellulose, 5 g twice a day	33	1.6	230.9	35.9	84.5
Methyl cellulose, 5 g twice a day, taken as a jelly	8	1.6	232.1	40.8	82.4

for their controls. This difference seems too large to be due to accidental variation. It probably resulted from a lower food intake, since the medicated females ate only 12.2 g a day, which contained 11.0 g of the Tioga meal, as compared to 13.9 g for the controls. On a percentage basis the medicated females ate 79.9% of the food, but gained 85.8% as much weight as the controls. Hence, it appears that the medicated rats gained more than would be predicted from their food intake.

At the end of 95 days of feeding, the rats were sacrificed, autopsied and the tissues examined microscopically.† In Table I it can be seen that there was no demonstrable change in the weights of the heart, liver, spleen and kidneys. The stomachs of the methyl cellulose animals were 15% heavier than the controls, an observation made previously for other bulky diets in this department and elsewhere.[6,7] There were no significant microscopic changes which would indicate any toxic effect of the methyl cellulose on the visceral organs examined.

Laxative Effects in Man. Methyl cellulose 4000 c.p.s. was taken in various combinations with magnesium oxide powder and finely milled bran, and also alone by 3 subjects in the form of fine flakes. All subjects maintained a constant diet and collected their stools quantitatively. These were weighed before and after drying to a constant weight at 110°C. One to 2 weeks as control periods were alternated with medication periods of the same length. The combined summarized results are given in Table II.

The average wet weight of stools on the control days was 127.4 grams with approximately one evacuation a day. When methyl cellulose was mixed with various proportions of a finely milled bran, or with 3.5 or 10% of magnesium oxide, the number and volume of the stools were moderately increased. However, the results indicated that the amount of methyl cellulose administered was more important than the other materials in the quantities used. Methyl cellulose alone in a dose of 5 g twice a day increased the

† The microscopic studies were performed by Dr. A. J. Cox, Jr., professor of pathology, Stanford University School of Medicine.

[6] Addis, T., *Am. J. Physiol.*, 1931, **99**, 417.

[7] Tainter, M. L., Kulchar, G., and Stockton, A. B., *J. Am. Pharm. Assn., Scientific Edition*, 1942, **29**, 306.

number of stools to 1.6 a day and the wet weight to an average of 232.1 g a day. This represented a stool volume almost double the normal. The methyl cellulose stools had a slightly higher water content than the controls, and were semi-soft and easy of passage. No colicy or griping pains were experienced as a result of the drug administration.

The averages indicated that each gram of methyl cellulose ingested increased the bulk of the stools about 10 g. The greater part of this increase was water held by the colloid, although the dry weight increased somewhat more than could be accounted for by the dry weight of the methyl cellulose administered. Comparison of these results with those previously reported with gum karaya and psyllium[5] showed that gram for gram methyl cellulose had greater effect than these others. It would, therefore, seem to merit more extensive laboratory and clinical investigations.

The observations here reported are not enough in themselves to establish the clinical usefulness of this material. The toxicity studies carried on were not extensive enough to establish its safeness for repeated human consumption. For instance, the possibility of splitting off of the toxic methoxy groups in the body should be considered. It should be tested clinically in a variety of dysfunctions of the gastrointestinal tract to explore its general usefulness. Since it is not possible to continue these studies, the data obtained are presented in their present form for the value they may have to others interested in this problem.

Conclusions. 1. Methyl cellulose is a synthetic material having physical and chemical properties which would make it suitable for use as a colloid laxative. 2. Feeding it in a 10% concentration in the diet of rats, so they ingested an average of 11.4 g per kilo daily for 95 days, caused no change in the growth rate of the males, but decreased the growth of females about 14%, apparently as a result of decreased food intake. There were no significant pathological changes in the medicated animals observed at autopsy. 3. In doses of 10 g a day methyl cellulose approximately doubled the volume of the stools and increased their frequency in normal human subjects, a desirable clinical result sought by the use of colloidal laxatives. Each gram of methyl cellulose ingested increased the stools approximately 10 g. 4. Both the toxicological and clinical studies should be extended before a general therapeutic use of the drug as a laxative is approved.

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Action of Antibiotic Substances Upon *Ceratostomella ulmi.**

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The ability of certain antibiotic agents to exert selective fungistatic and even fungicidal properties has been definitely established. This is true particularly of gliotoxin,[1] actinomycin[2] and hemipyocyanin.[3] The purpose of this investigation was to determine the effect of various antibiotic substances upon *Ceratostomella ulmi*, the causative agent of the Dutch elm disease. This problem represents two significant aspects: (a) the economic importance of this organ-

* Journal Series Paper, New Jersey Agricultural Experiment Station, Rutgers University, Department of Soil Microbiology.

1 Weindling, R., and Emerson, O. H., *Phytopath.*, 1936, **26**, 1068; 1937, **27**, 1175.

2 Waksman, S. A., and Woodruff, H. B., *J. Bact.*, 1941, **42**, 231.

3 Stokes, J. L., Peck, R. L., and Woodward, C. R., PROC. SOC. EXP. BIOL. AND MED., 1942, **51**, 126.