

Evaluation of Flu-Like Symptoms in Workers Handling Xanthan Gum Powder

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A study was performed to determine the relationship between the handling of xanthan gum powder and reported symptoms. Nose and throat irritation was the most prevalent symptom, and the group with the greatest exposure reported the highest prevalence of nose and throat irritation as well as work-related illness. Employees who reported illness as a result of exposure to materials at work did not show a decrease in pulmonary function over the first day of the workday or workweek. There was no evidence of chronic loss of pulmonary function in employees with either the highest or longest exposure.

Xanthan gum, a high molecular weight polysaccharide, is a hydrocolloid widely used in the food industry as a stabilizer and thickener, in the cosmetic industry to suspend and thicken ointments and creams, in oil drilling as a lubricant, and in the pharmaceutical industry as an excipient in manufactured tablets. It is fermented from corn syrup by *Xanthomonas campestris*, then precipitated by isopropyl alcohol, dried, milled, and packaged. It contains α -glucose, α -mannose, and α -glucuronic acid as the dominant hexose units and is manufactured as the mixed salt of potassium, magnesium, and calcium.¹ Bulk xanthan gum contains approximately 4-5% proteinaceous material derived from the *X. campestris*.

There is no body of literature pertaining to the occupational health hazards associated with handling xan-

than gum. It is a nontoxic compound, particularly by the oral route.¹ Acute skin and eye irritation tests indicate that the compound is nonirritating² and is negative in an intracutaneous guinea pig sensitization test. However, xanthan gum has been shown to induce proliferation of mouse B lymphocytes and thymocytes in vitro with concomitant antibody synthesis.³

During the more than 20 years of xanthan gum production, there have been sporadic reports of "flu-like" symptoms in workers handling xanthan gum powder. Information on the frequency, severity, and duration of the symptoms has been for the most part anecdotal. The symptoms are variable but most frequently have been described as chest tightness or heaviness, cough, and a self-limited flu-like response.

Most of the anecdotal reports of symptoms received were from new employees or employees who had not previously worked with xanthan gum. In one specific incident, involving a xanthan gum fire and related cleanup, 10 of 14 employees working during the incident complained of varying degrees of fever, chills, aches, nausea, and chest tightness. Cough was also reported but was rare. One employee with additional symptoms of vomiting, joint pain, increased pulse rate, and elevated white blood cell count was diagnosed as having an acute illness consistent with hypersensitivity pneumonitis. Because of the severity of the reaction and diagnosis, this is considered an index case.

Hypersensitivity pneumonitis is an allergic lung disease that results from the sensitization and repeated inhalation of a wide variety of organic dusts, including: cotton, flax and hemp,⁴ guar gum,⁵ gum arabic,^{6,7} and egg protein.⁸ There are several clinical stages associated with hypersensitivity pneumonitis.⁹ When intermittent exposure to offending antigens is intense, symptoms begin abruptly within several hours of exposure and typically include fever, chills, tiredness, dry cough, increased breathing rate, chest sounds, and increased

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0098-1736/90/3307-0625\$03.00/0

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white blood cell count. In addition, a decrease in forced vital capacity and forced expiratory volume in 1 second with a constant ratio between these parameters is seen. Expiratory flow rates are not as greatly affected. All these changes are reversible and subside usually within 12 to 18 hours. When exposure to offending antigens is less intense, chills and fever do not occur. Cough is less frequent. Pulmonary function changes are often detected, however, even in asymptomatic phases of the disease. In the chronic form of the disease, symptoms are primarily respiratory in nature and include progressive shortness of breath, weight loss, and cough with sputum. Acute episodes do not occur as frequently in patients with the chronic form of the disease. Late stages of the disease may include diffuse interstitial fibrosis visible on a chest roentgenogram. Generally, the later stages of the disease are partly reversible.

A study was performed to determine the relationship between the handling of xanthan gum powder and reports of flu-like symptoms and/or hypersensitivity pneumonitis. Specifically, a medical evaluation was performed to determine the nature and prevalence of flu-like symptoms, whether or not subsymptomatic effects are evident that are detectable by pulmonary function tests, and to examine for evidence of chronic pulmonary effects in workers exposed to xanthan gum powder. In addition, a joint industrial hygiene survey was performed to determine the potential for exposure to xanthan gum powder under normal operating conditions.

Methods

Study Population

All employees with potential exposure to xanthan gum powder were identified and grouped according to the average percentage of time spent in the plant, not the expected intensity of exposure to xanthan gum dust. The exposure groups were group A, exposed 60% to 100% of the time; group B, exposed 20% to 60% of the time; group C, exposed 1% to 20% of the time; and group D, exposed less than 1% of the time. Finally, the unexposed cohort, group E, was chosen from areas that are remote from the xanthan gum manufacturing site. They included employees from the personnel, purchasing, engineering, and administration departments whose structural environments are separate buildings, usually offices.

A description of the exposure groups by age, sex, current smoking status, percent of time spent in the plant, and length of employment is provided in Table 1. The employees in group A are all employed at entry-level operator positions in the plant. The employees in this group are, on the average, significantly younger than those in the other exposure groups and tend to have smoked less. Group A also was employed for a significantly shorter length of time. Group B employees tended to be older than those in the other exposure groups and had been employed for a significantly longer period than group A employees. Group B employees were either senior-level operators or supervisors in the plant. Group C employees were generally mechanics and engineers who entered the plant on an infrequent but daily basis. Group D employees were primarily chemists and engineers who occasionally came in contact with xanthan gum and rarely entered the plant. These employees generally tended to be older and to have worked longer at the site.

Medical History Questionnaire

To obtain the necessary medical history and information on the prevalence of symptoms related to exposure to xanthan gum, a specific questionnaire was developed. The questionnaire was modified from the interval medical history form normally used by Corporate Employee Health Services. Questions concerning pulmonary, cardiac, and skin allergy conditions were included. Additional questions pertaining to previously reported xanthan gum-related symptoms were also included. Occupational and smoking histories were obtained for each employee. In addition, each employee was asked whether or not any of the symptoms were thought to be the result of exposure to materials at work. The questionnaire was self-administered and results were entered into a computerized occupational health information system data base for analysis.

Physical Examination

Each employee was examined just before the pulmonary function tests. On the morning of the first day of pulmonary function testing, measurements of pulse, respirations, blood pressure, and temperature were taken. Chest auscultations were also performed on each subject.

TABLE 1
Description of Study Population by Exposure Group

	Exposure Group				
	A (n = 9)	B (n = 7)	C (n = 11)	D (n = 12)	E (n = 42)
Age (y), mean $\pm$ SEM	33 $\pm$ 3.4	41 $\pm$ 2.8	39 $\pm$ 2.1	39 $\pm$ 3.4	42 $\pm$ 1.6
Sex ratio (M:F)	5:4	6:1	10:1	10:2	28:14
Present smokers	3 (33%)	3 (43%)	4 (36%)	3 (25%)	8 (19%)
Tobacco consumption (pk-y)	8	22	22	15	14
% Time in plant	60-100	20-60	1-20	1	0
Average length of employment (mo)	13.5	129.8	111.5	111.6	-

Immunological screening tests were considered but were not included in the study protocol because preliminary tests to detect a specific antibody response to xanthan gum, in the index case and in rabbits, were negative. Precipitating antibodies to xanthan gum were not detected in serum from the index case using a double-diffusion technique in agar gel. Various dilutions of xanthan gum and patient serum were reacted to exclude the possibility of a false-positive or false-negative result as a consequence of antigen or antibody excess. Two rabbits were injected with RIBI adjuvant and xanthan gum twice over 2 weeks. However, the animals did not develop any precipitating antibodies to xanthan gum. To assess further the immunogenicity of xanthan gum, two rabbits were injected with Freund's adjuvant and xanthan gum and two other rabbits were injected with modified Freund's adjuvant and xanthan, both on two occasions over 2 weeks. No precipitating antibodies to xanthan gum were detected in any of the rabbits. An ELISA antibody assay was not developed to assay for the presence of other antibodies that might not precipitate.

Pulmonary Function Testing (PFT)

Pulmonary function was measured using a Vitalograph S model dry bellows spirometer (Kansas City, MO) with a PFT printer. Each employee was asked to perform three forced expiratory maneuvers to determine the following: the forced vital capacity (FVC); 1-second forced expiratory volume (FEV_{1.0}); peak expiratory flow rate (PEF); and forced expiratory flow (FEF) at 25% to 75% of total lung volume. Two of the maneuvers had to be within $\pm 10\%$ to be acceptable, and the pulmonary function parameters were calculated from the best of the maneuvers.

Changes in FVC, FEV_{1.0} and flow rate are clinical features of hypersensitivity pneumonitis; thus, these end points were selected for study. Also, FVC and FEV_{1.0} changes have been described in other studies of occupationally induced hypersensitivity pneumonitis.¹⁰ To determine the acute respiratory effects of xanthan gum on pulmonary function, testing was performed in four sessions: in the morning and afternoon of both the first day of the workweek and the last day of the workweek. Because the employees worked staggered shifts, the first day of the workweek did not always fall on a Monday. Because previous measures of pulmonary function were not available for all employees, the morning pulmonary function of the first day of the workweek was used as a measure of baseline function. To ensure that this baseline function was measured after at least 2 days away from work and to ensure that the PFT was performed on the day shift, the testing had to be staggered over a 2-month period. Seasonal and climatic conditions did not vary significantly over this period. The employees worked a 5-day workweek and pulmonary function was

tested on the last day of the workweek. These results were compared to determine the acute changes in pulmonary function within each day and over the workweek.

The results of the first day morning pulmonary function tests were compared with predicted values based on age, sex, height, and race as generated by Knudson et al.¹¹ A statistical comparison of the unexposed control (group E) with the exposed (groups A to D), in terms of mean percent of predicted value, was performed to determine possible chronic or long-term effects of xanthan gum. To make this comparison it had to be assumed that all workers were within "normal range" before employment and that any deviations from normal were the result of exposure to agents in the workplace over the period of employment. All statistical comparisons of pulmonary function test results were performed using the SAS *t* test procedure comparing two groups with equal variances.¹²

Constant conditions were maintained throughout the period that pulmonary function tests were performed. Ambient daytime temperature was approximately 78°F and did not vary significantly from morning to afternoon. All pulmonary function testing was performed in an on-site air-conditioned Health Services facility. The starting times and finishing times were the same on both days of testing. Each subject was required to wear noseplugs while being tested. Equipment volume was calibrated before each pulmonary function test session by injecting a known volume of air through the mouthpiece and reading the results. Deviations from calibration were minimal.

Environmental Survey

Because an objective of the study was to correlate the measurable effects of xanthan gum on the health of employees with the respirable components of their work environments, an air-sampling program was conducted to characterize exposures. This was done during the same period covered by the pulmonary function testing, primarily to assure that any responses can be correlated to concurrent exposure.

The plant that was studied uses a fermentation process to convert corn syrup to xanthan gum using *X. campestris*, which, after precipitation, yields a light-yellow fibrous mass that is dried, milled, packaged, and sold as xanthan gum. The exposure of interest in this study is the fermentation product after it is harvested, dried, milled, and packaged. The fermenters are located outside and the precipitators and dryers are located in a roofed structure with incomplete walls. Milling, blending, and packaging are done in a closed building. These latter activities presented the dust exposure of greatest concern. There are no established exposure limits for xanthan gum or for any other gum for that matter. The current recommendation followed at the plant and throughout the industry is an 8-hour time-weighted average nuisance dust level of 10 mg/m³ total dust or 5 mg/m³ respirable dust. This level is supported by Cali-

California Occupational Safety and Health Administration in response to a special study done from 1975 to 1977.

The sampling pumps were all Gilian 113A High Flow pumps with cyclone precollectors to collect only respirable dust. The decision to monitor respirable dust only was based on the fact that the effect being evaluated is believed to be the result of inhalation of particles into the lung. It was decided that larger particles would impinge upon the upper respiratory tract and, therefore, would have no lower respiratory tract effects. The filter cassettes were three-piece, shrink-banded units containing preweighed AE filters. The filters were first aged for 48 hours at 70°F and 50% relative humidity, then weighed to the nearest microgram on a Cahn 4700 Electrobalance. The pumps were calibrated before and after each sample using a Kurz 1504 mass flow hot wire anemometer. On the first day of sampling, the Kurz meter was calibrated against a 1.0-liter bubble meter.

A list of job titles to be sampled was prepared before commencing the study. The workers were preselected from day-shift schedules. In all, 48 samples were of the personal type and 14 were area type. Of the 14 area samples, two pairs were identical except that one was taken with a cyclone precollector and one was taken without. The people were informed of the purpose of the study and the need to report any unusual conditions that occurred. The intent was to sample normal operations. Each person was sampled for essentially a full shift and each was checked several times during that shift to be sure the pump was operating properly. When an employee had more than one personal sample taken, the mean of the samples was used.

Exposed filters were aged for 48 hours at 70°F and

50% relative humidity and reweighed. The concentration was corrected for the temperature and barometric pressure that prevailed as of 12:00 noon on the day of sampling. Results were reported in mg/m³.

Results

Table 2 shows the prevalence of acute symptoms in each of the exposure groups. Nose and throat irritation and cough were the most prevalent symptoms historically reported. The prevalence of nose and throat irritation was highest in group A, whereas the highest percentage of group C employees reported cough. Skin allergies were reported by employees in all exposure groups. However, employees did not relate these to exposures at work. Frequent flu or cold symptoms were not generally reported. Exposure group A reported the highest prevalence of work-related illness and exposure groups A, B, C, and D reported a higher prevalence of work-related illness than control group E.

A further analysis of the work-related symptoms showed that five of the seven group A employees reported having experienced work-related symptoms of the respiratory tract. These included flu-like symptoms, chest heaviness, and shortness of breath. One of the five employees reported that the symptoms were due to other chemical exposure. In the remaining groups, work-related symptoms were either respiratory tract or dermatological. In control group E, it was found that the majority of reported respiratory symptoms were unrelated to work.

Table 3 shows the pre-exposure pulmonary function by exposure group. The pulmonary function test results from the morning of the first day of the workweek are used. FVC, FEV_{1.0} and PEF are expressed as a percentage of predicted values, which corrects for age, sex, height, and race. The FEV_{1.0} as a percentage of FVC is also shown. None of the differences between exposure groups is statistically significant. Seventeen employees were identified as having FEV_{1.0}/FVC percents less than 75%. This is the criterion by which the American Thoracic Society defines mild impairment of pulmonary function.¹³ Of the 17 employees identified, 12 were past or present cigarette smokers. Of the five nonsmokers, two had cold symptoms at the time of pulmonary function testing. Only four of these 17 employees reported workplace reactions.

TABLE 2
Prevalence of Symptoms by Exposure Group

Symptom	Exposure Group				
	A (n = 9)	B (n = 7)	C (n = 11)	D (n = 12)	E (n = 42)
Nose, throat irritation	6	0	3	1	14
Cough	5	2	6	4	20
Frequent flu or colds	2	1	2	1	4
Wheezing	1	0	4	0	3
Shortness of breath	1	2	2	0	5
Chest tightness	2	0	2	0	7
Joint pain	2	0	4	2	11
Skin allergies	1	2	5	5	14
Work-related illness	7	2	5	5	7
Chemical exposure	2	2	7	1	13

TABLE 3
Pre-exposure Pulmonary Function By Exposure Group

	Exposure Group*				
	A (n = 9)	B (n = 7)	C (n = 11)	D (n = 12)	E (n = 42)
FVC, % Predicted†	104 ± 4.6	94 ± 4.8	98 ± 3.2	95 ± 4.3	100 ± 1.8
FEV _{1.0} , % Predicted†	100 ± 4.5	86 ± 5.3	96 ± 3.4	89 ± 5.4	93 ± 2.1
PEF, % Predicted†	113 ± 7.1	97 ± 6.8	110 ± 3.8	95 ± 6.2	99 ± 6.3
FEV _{1.0} /FVC %‡	81 ± 1.0	76 ± 2.0	82 ± 1.5	78 ± 2.3	77 ± 1.2

* All values presented as mean ± SE of the mean.

† All values shown as mean average percent of predicted value.

‡ All values expressed as a mean percentage.

Figures 1 and 2 show mean pulmonary function as a percentage of the day 1 morning value for all five exposure groups. Figure 1, a and b, shows FVC and FEV_{1.0}, respectively whereas Fig. 2, a and b, shows FEF and PEF respectively. None of the exposure groups showed a statistically significant change over the first or last workdays or over the workweek. When the changes in groups A, C, and D were compared with controls (group E), the differences were not statistically significant. In group B, FVC, FEV_{1.0}, FEF, and PEF all decreased over the first day of the workweek. However, the decreases were not statistically significant. The decrease in FEF over the workweek was statistically significant ($P < .05$) when compared with controls (group E). No employee reported a greater than 15% reduction in FVC over the first day of the workweek, and only four reported a greater than 10% reduction in FVC over the first day of the workweek. Of these four, two were in control group E and two were in exposure group B. Two employees—one in control group E, the other in exposure group D—reported a 15% or greater reduction in FEV_{1.0} over the first day of the workweek, and four employees reported a 10% reduction in FEV_{1.0}

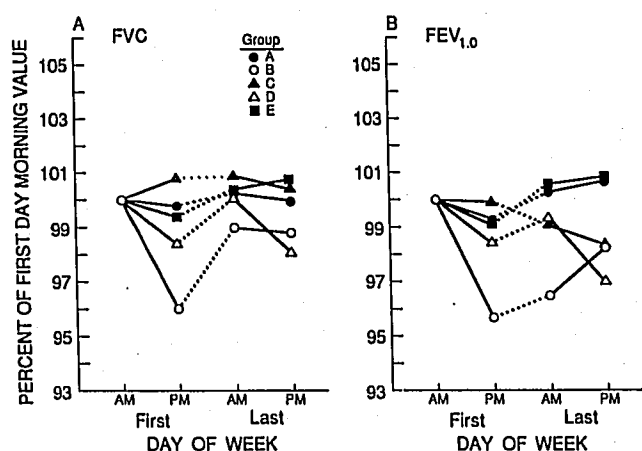


Fig. 1. FVC and FEV_{1.0} expressed as a percentage of the first day morning value for each of the five exposure groups.

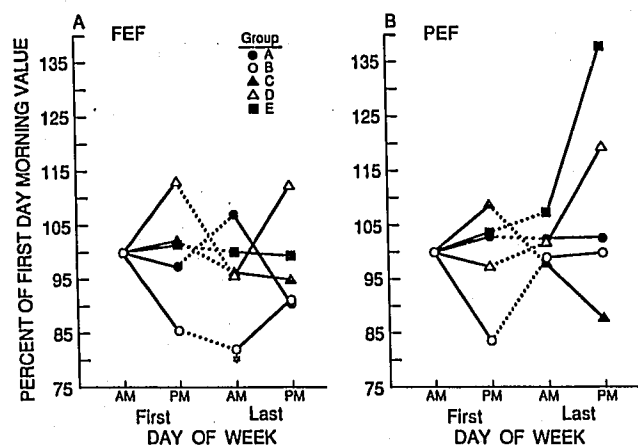


Fig. 2. FEF and PEF expressed as a percentage of the first day morning value for each of the five exposure groups.

TABLE 4
Average Breathing Zone Xanthan Gum Dust Concentrations by Exposure Group

Exposure Group	No. of Samples	Xanthan Gum Dust Concentrations, 8-hr TWA, mg/m ³	
		Mean $\pm$ SEM	Range
A	14	0.54 $\pm$ 0.71	0.11–1.91
B	9	0.15 $\pm$ 0.36	0.00–0.39
C	12	0.08 $\pm$ 0.39	0.00–0.46
D	9	0.04 $\pm$ 0.22	0.00–0.13

over the first day of the workweek. The remaining two employees were from group B.

Changes in pulmonary function over the first day of the workweek and the entire workweek were examined for plant workers with and without respiratory symptoms related to work. Employees relating any symptom reported in the questionnaire to a chemical exposure at work were classified as symptomatic for the purposes of this evaluation. All other plant employees were considered asymptomatic. No differences between the symptomatic group and the asymptomatic group were statistically significant. A further analysis was performed to determine whether any sex differences existed in the group reporting symptoms compared with those who did not. No statistically significant sex differences were found.

Changes in pulmonary function over the first day of the workweek and the entire workweek in plant workers were examined by current smoking status. In general, smokers experienced a greater fall in pulmonary function over the day and week. However, the differences between current smokers and nonsmokers were not statistically significant. An additional analysis was performed to determine whether there was a greater number of employees reporting symptoms among those who smoked than those who did not smoke. No statistically significant differences were found.

Table 4 shows the average and range for the results of the breathing zone samples for xanthan gum dust by exposure group and individual activity. A total of 44 breathing zone samples were taken. It can be seen that activities performed by group A operators in the plant milling area were associated with the highest dust concentrations, ranging from 0.11 mg/m³ to 1.91 mg/m³. Group A had the highest average breathing zone xanthan gum dust concentration, followed by groups B, C, and D, respectively. This is likely a reflection of the percentage of time spent in the milling area. Activities such as cleaning, milling, blending, bagging, and drumming are associated with the highest breathing zone dust concentrations. These are normal operations performed on a daily basis. There were no reports of abnormal events occurring during this study. Therefore, these dust concentrations represent the normal daily potential exposure of employees performing these operations.

The results of the area samples support the breathing zone sample results and indicate that the highest dust

concentrations were associated with milling of the xanthan gum. Area sample data also show that individuals in the control groups had no detectable exposure to xanthan gum dust.

Because the industrial hygiene surveys were performed on the first day of the workweek, a regression analysis of the change in pulmonary function as a function of breathing zone xanthan gum dust concentrations was performed. In cases where the employee wore respiratory protection while performing the activity, the dust exposure was assumed to be zero. Analysis of variance was performed using the SAS regression procedure.¹⁸ No correlation was found between the breathing zone xanthan gum dust concentrations and changes in FVC, FEV₁, FEF, and PEF over the first day of the workweek.

Discussion

The results of the questionnaire revealed that respiratory symptoms were reported by all exposure groups but that there was a slightly increased prevalence of nose and throat irritation and illness related to exposure to material at work in group A. However, no significant acute changes in pulmonary function were found in any of the exposure groups. Of the four exposure groups, group B revealed slight decreases in pulmonary function over the first day of the workweek. These changes, however, were not statistically significant and may possibly be accounted for by the increased average age of the group. Group A, which had the largest percentage of time in the milling area, demonstrated no significant change in pulmonary function over the day or over the week.

There were no differences in the number of cigarette smokers in each group and an analysis of pulmonary function revealed no significant differences between smokers and non-smokers in terms of decrease in pulmonary function over the day and the week.

The before and after approach could not be applied to the study of chronic exposure to xanthan gum because the results were based on pulmonary function measurements made during a single workweek and because there were no data to indicate the employees' lung function before employment in the plant. To circumvent this problem, a cross-sectional approach was used to predict longitudinal effects. The lung function measured on the morning of the first day of the workweek, after two days away from work, was considered the baseline function. For each worker, the data were compared to a prediction formula based on a normal population and presented as a percent of predicted value for each employee. A comparison of the mean percent of predicted values for each exposure group showed no evidence of a chronic or long-term effect.

This study revealed that no acute or chronic effects on pulmonary function from xanthan gum exposure could be measured. If acute effects were to be found, it was anticipated that they would be seen in workers in group A, which had the highest percentage of time spent in the millroom (60% to 100%), the highest average exposure to xanthan gum dust (0.1% to 1.9 mg/m³),

and a slightly increased prevalence of reported respiratory symptoms, even though they have been in the job the shortest period of time (13.5 months). However, no such acute effects were found. On the other hand, any chronic or long-term effects would be expected in group B, which had worked for the longest period of time in the millroom, but by virtue of their jobs, spent less time during the day in the millroom. No chronic long-term effects were revealed in this group.

Previous reports of flu-like symptoms generally followed abnormal events such as a baghouse fire or line failures, when operators were almost certainly exposed to transient, but unusually high, xanthan gum concentrations. Under current, normal operating procedures, no increase in reported symptoms and no acute or chronic effects on pulmonary function are evident. Therefore, current standard operating procedures and control measures including the use of the current nuisance dust standard should continue. If an abnormal event occurs, however, where there is increased potential for inhalation of xanthan gum dust, it is recommended that employees wear respiratory protection while performing any exposing operations such as repair and cleanup.

Acknowledgments

We thank the administration and employees of Kelco for their cooperation in this study; Mansoor Khan and the staff of the Merck Industrial Hygiene Laboratory for their analyses of air samples; Robert Dawson and Connie Shifter for assistance in air sampling; and Joan Feller for typing the manuscript.

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