Response of Human Lung Tumor Xenografts to Treatment with a Somatostatin Analogue (Somatuline)

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ABSTRACT

Four human small cell lung carcinomas, NCI-H69, NCI-N417, NCI-H345, LX-1, and a non-small cell lung carcinoma, H-165, implanted s.c. as tumor xenografts in athymic nude mice, were treated with Somatuline (BIM-23014C), an endocrinologically potent octapeptide analogue of somatostatin. All tumors responded, although in varying degrees, with percentage of test/control values ranging from 3 to 88. Somatuline administered as a perilesional infusion effectively inhibited xenograft growth inducing prolonged remissions. When treatment was terminated, some tumors regrew, suggesting antimitogenic activity rather than cytotoxic. Absence of observable systemic or local toxicity during prolonged treatment would support this conclusion and suggest the feasibility of long term maintenance therapy with a resultant extended survival.

INTRODUCTION

Abnormal growth factor production through autocrine or paracrine mechanisms may account, in part, for the ability of cancers to regulate their own growth rate. Although the action of a growth factor on target cells requires receptor expression, abnormalities of receptor function could result in abnormal cell proliferation. Also, postreceptor functions, which would normally only be triggered when receptors bind their ligands, can be activated by oncocenes and tumor promoters (1, 2). Such factors favor the uncontrolled growth of malignancies. However, cells in serum or in the body are exposed to a number of factors favoring or inhibiting cell proliferation. The interplay between these factors may be SRIF, initially described as an inhibitor of pituitary GH secretion and pancreatic insulin and glucagon secretion, as well as gastrointestinal and pancreatic exocrine secretions (3, 4). Results of studies in which a number of animal and human tumors of varied histology were screened for their responsiveness to the long acting SRIF analogue Somatuline (BIM-23014C) (5), support published reports indicating that SRIF analogues may have direct antiproliferative actions in both endocrine (6–12) and nonendocrine tumors (10, 12, 13) which appear to be independent of its growth hormone-inhibitory activity. SRIF may thus be classified as a neuroendocrine hormone which inhibits not only exocrine and endocrine secretions but also mitogenesis.

That several neuropeptides including neurotensin, epidermal growth factor, adrenocorticotropic hormone, calcitonin, neurokinin A, somatostatin, bombesin/GRP, and β-endorphin are produced by SCLC and cell lines derived from these tumors (14, 15) is well documented. Although receptors for only a few of these peptides have been characterized in some SCLC lines (14–17) it does suggest that specific peptides may regulate the growth of SCLC in an autocrine fashion similar to that of bombesin/GRP (18). The apparent dependence of growth on the secretion of autocrine growth factors suggests the therapeutic potential of somatostatin analogues in the treatment of SCLCs.

Initial in vitro studies of the human SCLC line NCI-H69 revealed membranes highly enriched with SRIF receptors (19). Subsequent studies to test whether SRIF could be SCLC growth inhibitory demonstrated that the long acting SRIF analogue Somatuline had antiproliferative activity for NCI-H69 both in vitro and in vivo (20, 21). To further test the hypothesis that SRIF could be a growth-inhibitory factor for SCLC, similar to that observed for endocrine tumors, Somatuline was tested against xenografts of additional SCLCs NCI-H345, NCI-N417, and LX-1 as well as against a NSCLC H-165. The results are the subject of this report.

MATERIALS AND METHODS

Tumors. The in vitro maintained human SCLC lines NCI-H69, obtained from the American Type Culture Collection, NCI-H345 and NCI-N417, graciously provided by Dr. A. Gazdar, were cultured in RPMI 1640 containing 10% fetal bovine serum and a humidified atmosphere of 10% CO2 and 90% air (37°C). The human SCLC LX-1 and squamous cell lung carcinoma H-165, maintained in our Tumor Bank, were propagated in vivo as xenografts in immunodeficient athymic nude mice.

Histologically a poorly differentiated carcinoma, LX-1 was derived and established in serial transplantation by B. Giovanella from a biopsy specimen of a metastasis to the s.c. tissue of the right arm. The primary tumor was an inoperable small cell carcinoma of the left lung of a 48-year-old male. The tumor had been unresponsive to treatment with cyclophosphamide + radiation + Corynebacterium parvum immunotherapy. A relatively fast growing tumor with a transplant interval of only 15 to 20 days, LX-1 was selected to more rigorously test the somatostatin analogue against human SCLC xenografts prepared from transplantation-established human tumors.

In an earlier study we found LX-1 to be responsive to Somatuline in an 11-day subrenal capsule assay in which Somatuline was administered s.c. and the tumor implanted under the renal capsule. Since tumor sensitivity to Somatuline administered away from the tumor had been demonstrated previously, in the present study only the s.c. and i.p. routes of administration of Somatuline were tested.

Diagnosed as a non-small cell carcinoma with squamous metaplasia, H-165 was obtained as a surgical explant from the upper left lobe of a 73-year-old female and established in serial transplantation by A. E. Bogden. Histologically it is a moderately pleomorphic population com-
posed of epithelial cells, predominantly in nests and also in sheets, supported by dense fibrovascular stroma. Cells are elongated or polygonal with eosinophilic cytoplasm. Nuclei vary in shape and size with chromatin and a nucleolus. Mitotic figures are numerous.

Inclusion of a NSCLC for testing was prompted by reports of EGF receptor gene amplification in primary tumor specimens of squamous cell lung carcinomas (22-25) and the demonstration that somatostatin inhibited EGF-induced DNA synthesis and cell replication via an inhibition of the EGF-induced centrosomal separation, a biological marker of G1 phase in cycling cells (26).

Tumors were measured two or three times weekly with Vernier calipers and tumor size calculated as the average of two diameters (length + width/2) mm. Levels of significance were determined using Student’s t test.

Animals. Female Hsd: athymic NCr-nu mice were used for carrying tumors in serial transplantation as well as for testing.

In Vivo Testing. The in vitro-maintained SCLC lines, which grow in suspension as cellular agglomerates of various sizes, were collected by low speed centrifugation and resuspended in culture medium, and equal aliquots were injected s.c. into the right flank of female athymic nude mice. To minimize cell membrane perturbation, no attempt was made to physically or chemically disaggregate the cellular agglomerates. A s.c. inoculum of NCI-H69, NCI-H345, or NCI-N417 cells consisted of the contents of 5 confluent 75-cm2 flasks administered in a packed volume of 0.2 ml. A confluent flask has a volume of approximately 60 ml containing 5 × 10^6 cells/ml or 15 × 10^7 cells/inoculum.

In vivo propagated tumor lines were excised from donor animals, minced, and implanted s.c. as 2-3-mm cubed xenografts into the right flank of female athymic nude mice. Tumor-implanted animals were then individually identified and randomized into control and test groups.

Somatuline was administered in a saline vehicle either i.p., s.c. on the side opposite of the tumor, or s.c. as an infusion around the tumor. Care was taken not to inject i.l. Treatments were administered twice daily, Monday through Friday, and as a single total daily dose on weekends. Length of treatment varied with the tumor.

SRIF Receptor Binding Assay. Crude membrane preparations were obtained by homogenizing (Polytron, setting 6, 15 s) the SCLC tumors in ice-cold 50 mM Tris-HCl and centrifuging twice at 39,000 × g (10 min), with an intermediate resuspension in fresh buffer. The final pellets were re suspended in 10 mM Tris-HCl for assay. Aliquots of the membrane preparation were incubated for 25 min at 30°C with 0.05 mM [3H]SRIF-14 (2000 Ci/mmol; Amersham Corp.) in 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (pH 7.4) containing bovine serum albumin (10 mg/ml; fraction V, Sigma Chemical Co.), MgCl2 (5 mM), Trasylol (200 kallikrein inhibitor units/ml), bacitracin (0.02 mg/ml), and phenylmethylsulfonyl fluoride (0.02 mg/ml). The final assay volume was 0.3 ml. The incubations were terminated by final assay volume was 0.3 ml. The incubations were terminated by addition of 2 ml of 10 mM Tris-HCl buffer. The samples were then washed three times with 5-ml aliquots of ice-cold buffer. Specific binding was defined as the total [3H]SRIF-14 bound minus that bound in the presence of 200 nM unlabeled SRIF-14.

Somatuline (BIM-23014C, DC13-116), a long acting octapeptide analogue of SRIF, has the structure (20)

\[\text{[d-\beta-Nal-Cys-Tyr-d-Trp-Lys-Val-Cys-Thr-NH}_2\text{]}\text{ acetate}\]

RESULTS

NCI-H69 SCLC. Initial demonstration of the in vivo inhibitory activity of SCLCs by Somatuline was obtained by treating cell aggregates that had been taken from in vitro culture and implanted s.c. as first transplant generation xenografts in athymic nude mice (21). Therefore, the objective of the present study was to confirm the in vivo antitumor activity of Somatuline by more stringent testing against NCI-H69 tumor xenografts derived from a solid tumor donor, i.e., tumors in the second in vivo transplant generation.

Somatuline, at a 500-µg/injection dose, was administered in a volume of 0.2 ml s.c. on the side opposite of the tumor or s.c. as an infusion around the tumor twice daily, except on weekends when the total daily dose was administered in one injection. Treatment was initiated in the afternoon of the day of tumor implantation and continued for 40 days. Final tumor sizes on day 40 are shown in Table 1 and the resultant tumor growth curves illustrated in Fig. 1.

The growth of second in vivo transplant generation xenografts was relatively slow, vehicle-treated controls reaching an average diameter of 5.75 mm over the 40-day assay period. Although all xenografted animals did not develop tumors measurable with Vernier calipers, there was no culling. The percentage of tumored animals in each group on day 40 is shown in Table 1. Not only were there fewer tumors in the Somatuline-treated groups, but the tumor sizes were smaller. Administration of Somatuline as a s.c. infusion around the tumor was most effective inhibiting tumor growth (Fig. 1) emphasizing the importance of the somatostatin analogue reaching the tumor site in therapeutic concentrations.

NCI-N417 SCLC. Efforts to establish the in vitro cultured cell line NCI-N417 as an in vivo propagated tumor were unsuccessful. Therefore, NCI-N417 SCLC cells were tested as first transplant generation xenografts implanted in athymic nude mice. The tumor take rate of this cell line in vivo is not 100% necessitating a culling of no-takes. The criteria for such selection was as follows. On day 49 at termination of the assay, the tumor size records of all animals having no palpable tumor nodes at the implant site were reexamined. Animals with no palpable or measurable tumor nodules at the implant site on both days 14 and 49 were considered as no-takes and were culled from the assay. In each test group of six animals that were originally implanted, there were two animals considered as no-takes. Note in Fig. 2 that the nadir of control tumor size is on day 14; thereafter growth was progressive.

Somatuline was administered s.c. on the side opposite of the tumor or s.c. as an infusion around the tumor at a 500-µg/ injection dose twice daily except on weekends when the total daily dose was administered as one injection, beginning on day 1, i.e., the day following tumor implantation and continuing for 49 days. The response of NCI-N417 tumor xenografts to Somatuline is summarized in terms of tumor size and number of tumored animals on day 49 (Table 2) and illustrated as growth curves in Fig. 2. NCI-N417 tumors were significantly responsive (P < 0.05) only when Somatuline was administered s.c. as an infusion around the tumor. Responsiveness was evident in terms of both tumor size as well as number of tumored animals remaining in each group on day 49.

NCI-H345 SCLC. This cell line is a classical GRP-secreting lung tumor when propagated in in vitro culture. It has abundant bombesin and neuropeptide receptors. Similar to the NCI-H69, Somatuline potently inhibited 125I-SRIF-14 binding (50% inhibitory concentration, 6 nM) although the receptor concentration appeared to be less than that found on the NCI-H69 cell line. However, the effect of cell culture conditions (e.g., passage number, etc.) have not been thoroughly studied in comparative assays with respect to somatostatin receptor concentrations. NCI-H345 is also a much slower growing tumor than NCI-H69, both in vitro and in vivo (27, 28).

NCI-H345 cellular agglomerates were transplanted from in vitro culture into athymic nude females on day 0. Treatment with Somatuline at 500 µg/injection, s.c. on the side opposite of the tumor, or s.c. as an infusion around the tumor, was initiated in the afternoon of the same day and continued twice
INHIBITION OF HUMAN SCLCs AND NSCLC BY SOMATULINE

Table 1  Response of second transplant generation NCI-H69 SCLC xenografts to Somatuline

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment*</th>
<th>Tumor size, a</th>
<th>% test/ control</th>
<th>No. of tumored animals/</th>
<th>% tumored</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle control, 0.2 ml/injection s.c. on the side opposite of tumor, b.i.d. q.d. 0-40</td>
<td>5.75 ± 1.4</td>
<td>5/10</td>
<td>7/10</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Somatuline, 500 µg/injection s.c. on the side opposite of tumor, b.i.d. q.d. 0-40</td>
<td>2.60 ± 1.9</td>
<td>45</td>
<td>1/5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Somatuline, 500 µg/injection s.c. as an infusion around the tumor, b.i.d. q.d. 0-40</td>
<td>1.60 ± 0.8*</td>
<td>28</td>
<td>2/5</td>
<td></td>
</tr>
</tbody>
</table>

* Treatments b.i.d. Monday–Friday and total daily dose in one daily injection on weekends.

(Length + width/2)mm presented as means ± SEM.

Number of animals with tumor/number of animals implanted.

b.i.d., twice a day; q.d., every day.

* Significance of difference from control, by Student’s t test, P < 0.05.

Administration of Somatuline s.c. on the side opposite of the tumor induced no tumor growth-inhibitory effects during the 99-day treatment period (Table 3). All animals in this group eventually developed measurable s.c. tumor masses. One animal with tumor died on day 128, i.e., 29 days after the last treatment. Following cessation of treatment, however, there is suggestion of accelerated growth (Fig. 3). The growth curve of the control group illustrates the extremely slow growth rate in vivo of this tumor system. All animals in this group developed tumors with one tumored animal dying on day 168.

A significant tumor growth-inhibitory effect was induced when Somatuline was administered s.c. as a perilesional infusion. The originally measurable s.c. tumor masses regressed until they were barely palpable by day 30 (Fig. 3). Tumor regrowth was inhibited during the entire treatment period. At cessation of treatment on day 87, two of the five animals had no palpable tumors (Table 3). In the three tumored animals, one tumor was barely measurable, < 3.0 mm average diameter, and two tumors were just palpable nodes.

In view of the almost complete and sustained regression of tumor xenografts in Group 3 animals treated perilesionally (Fig. 3), treatment was terminated on day 87, but periodic tumor measurements were continued for an additional 76 days. On day 113, i.e., 26 days after the last treatment by s.c. infusion, tumors in three of the five animals began a very slow but progressive regrowth. Tumor sizes in all three groups are compared in Table 3. After 76 days of no treatment, there still remained a highly significant difference in tumor size in the infusion-treated animals. There is a suggestion that two of the five animals in the group may have been “cured.”

LX-1 SCLC. The response of LX-1 to Somatuline administered at 500 µg/injection, twice a day except for weekends when the total daily dose was administered as one injection, is summarized in Table 4 and illustrated as growth curves in Fig. 4. Somatuline treatment initiated the day following tumor implantation induced a significant (P < 0.01) inhibition of tumor growth when administered s.c. on the side opposite of tumor. Administration i.p. was not as tumor growth inhibitory. Indication of a somewhat abrupt retardation of the growth of control tumors on day 26 (Fig. 4) is an artifact resulting from ulcerating tumors. Tumors in s.c.-treated animals had not ulcerated and showed a plateauing of the growth curve which would suggest the induction of stable disease.

H-165 NSCLC. H-165 was selected as a human lung tumor xenograft system representative of NSCLC and because, like LX-1, it is well established in serial transplantation in athymic nude mice. To make testing even more rigorous, treatment with Somatuline was not initiated until s.c. xenografts were well...
INHIBITION OF HUMAN SCLCs AND NSCLC BY SOMATULINE

Table 2 In vivo response of the human SCLC NCI-N417 to Somatuline

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment*</th>
<th>Tumor size, mm</th>
<th>% test/control</th>
<th>No. of tumored animals</th>
<th>% tumored</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle control, 0.2 ml s.c. as an infusion around the tumor, b.i.d. q.d. 1-49</td>
<td>19.2 ± 1.64</td>
<td>192</td>
<td>4/4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Somatuline, 500 µg/injection s.c. on the side opposite of tumor, b.i.d. q.d. 1-49</td>
<td>23.5 ± 1.39</td>
<td>235</td>
<td>4/4</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Somatuline, 500 µg/injection s.c. as an infusion around the tumor, b.i.d. q.d. 1-49</td>
<td>4.6 ± 4.6</td>
<td>46</td>
<td>1/4</td>
<td>25</td>
</tr>
</tbody>
</table>

* Treatments b.i.d. Monday–Friday and total daily dose in one daily injection on weekends.
* Length + width/2 presented as means ± SEM.
* Number of animals with tumor/number of animals implanted.
* b.i.d., twice a day; q.d., every day.
* Significance of difference from control, by Student's t test, P < 0.05.

Fig. 3. Response of NCI-H345 SCLC xenografts to Somatuline administered at 500 µg/injection, twice a day, every day, days 0–92. Mean of five animals in control and test groups. Numbers in parentheses, number of measurable or palpable tumors/number of animals implanted. Rx, day treatment was terminated.

established as measurable tumors on day 22 postimplantation. Somatuline was administered s.c. at two dose levels on a twice a day schedule except for weekends when the total daily dose was given in one injection. The response of H-165 to Somatuline is summarized in Table 5 and illustrated as growth curves over a 71-day treatment period in Fig. 5.

Tumor response to high dose Somatuline was significant (P < 0.05). Tumor inhibition was slow in evolving, but the tendency of a therapeutically effective dose to induce a plateauing of the growth curve (Fig. 5) suggests the induction of stable disease.

Receptor Binding. In contrast to previous studies (19) with the NCI-H69 and our observations with the NCI-H345 cell line discussed above, only barely detectable levels of specific 125I-SRIF-14 binding were observed in LX-1, NCI-417, and H-165 cells or solid tumors. It is of interest to point out that although SRIF receptors were present on solid NCI-H69 tumors grown in vivo in the athymic nude mouse, the concentration was only about 10% of that observed in cell culture (19).

Local and Systemic Toxicity. Skin color and texture at s.c. injection sites and body weights were monitored as indicators of local and systemic toxicity. There was no evidence of skin reactions or tissue necrosis at sites of s.c. injection or infusion of Somatuline. All treated groups also showed body weight gain during the course of treatment.

DISCUSSION

The *in vivo* responsiveness of four human SCLCs and a NSCLC to Somatuline suggests a therapeutic potential for somatostatin analogues in the treatment of lung cancer. Athymic nude mice bearing s.c. tumors resulting from the implantation of *in vitro* propagated cellular agglomerates or fragments of *in vivo* propagated solid tumors, were given Somatuline s.c. on the side opposite of tumor, or s.c. as an infusion around the tumor, the latter to facilitate diffusion of peptide toward the tumor. The infusional method proved to be most effective, emphasizing the importance of developing therapeutic concentrations of Somatuline at the tumor site to compete successfully with paracrine and/or autocrine growth factors. Although one treatment series was administered i.p. in one study (Fig. 4), this route of administration is not recommended because of the tendency of somatostatin to cause constriction of the splanchnic circulation.

Table 3 Comparison of NCI-H345 tumor sizes at the completion of Somatuline treatment and after a subsequent period of no treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment*</th>
<th>Tumor size, mm</th>
<th>Tumor size, mm</th>
<th>Tumor size, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>day 92</td>
<td>day 163</td>
<td>day 163</td>
</tr>
<tr>
<td>1</td>
<td>Vehicle control, 0.2 ml s.c. as an infusion around the tumor, b.i.d. q.d. 0–87</td>
<td>10.3 ± 1.8</td>
<td>5/5</td>
<td>12.4 ± 2.3</td>
</tr>
<tr>
<td>2</td>
<td>Somatuline, 500 µg/injection s.c. on the side opposite of tumor, b.i.d. q.d. 0–92</td>
<td>11.6 ± 1.4</td>
<td>5/5</td>
<td>16.5 ± 1.9</td>
</tr>
<tr>
<td>3</td>
<td>Somatuline, 500 µg/injection s.c. as an infusion around the tumor, b.i.d. q.d. 0–87</td>
<td>0.3 ± 0.2</td>
<td>1/5</td>
<td>3.3 ± 1.3</td>
</tr>
</tbody>
</table>

* Treatments b.i.d. Monday–Friday and total daily dose in one daily injection on weekends.
* Tumor size reported in mm as means ± SEM.
* b.i.d., twice a day; q.d., every day.
* One animal in this group with tumor died on day 128.
* Significance of difference from control, Student's t test, P < 0.01.
INHIBITION OF HUMAN SCLC AND NSCLC BY SOMATULINE

Table 4 In vivo response of the human SCLC LX-1 to Somatuline

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Tumor size, % test/control</th>
<th>Tumor size, % test/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle control, 0.2 ml/injection s.c. on the side opposite the tumor, b.i.d., q.d. 1-26</td>
<td>18.7 ± 2.7</td>
<td>18.7 ± 2.7</td>
</tr>
<tr>
<td>2</td>
<td>Somatuline, 500 µg/injection s.c. on the side opposite the tumor, b.i.d., q.d. 1-26</td>
<td>13.9 ± 1.9</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Somatuline, 50 µg/injection s.c. on the side opposite the tumor, i.p., b.i.d., q.d. 1-26</td>
<td>16.6 ± 1.6</td>
<td>88</td>
</tr>
</tbody>
</table>

*Treatments b.i.d., Monday–Friday and total daily dose in one daily injection on weekends.

Table 5 In vivo response of the human NSCLC H-165 to Somatuline

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Tumor size, % test/control</th>
<th>Tumor size, % test/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle control, 0.2 ml/injection s.c. on the side opposite the tumor, b.i.d., q.d. 22-71</td>
<td>19.6 ± 1.8</td>
<td>19.6 ± 1.8</td>
</tr>
<tr>
<td>2</td>
<td>Somatuline, 500 µg/injection s.c. on the side opposite the tumor, b.i.d., q.d. 22-71</td>
<td>12.4 ± 1.3</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>Somatuline, 500 µg/injection s.c. on the side opposite the tumor, b.i.d., q.d. 22-71</td>
<td>16.6 ± 1.8</td>
<td>85</td>
</tr>
</tbody>
</table>

*Treatments b.i.d., Monday–Friday and total daily dose in one daily injection on weekends.

*Significance of difference from control, Student's t test, P < 0.01.

Fig. 4. Response of LX-1 SCLC xenografts to Somatuline administered at 500 µg/injection, twice a day, every day, days 1–26. Mean of ten animals in the control and five in test groups.

Fig. 5. Response of H-165 NSCLC xenografts to Somatuline administered at 50 and 500 µg/injection, twice a day, every day, days 22-71. Rx, day treatment was initiated. Mean of eight animals in the control and four in test groups.

If normal cell proliferation involves both autocrine and paracrine stimulatory phenomena and normal control of growth involves the differential response to tonic concentrations of several growth-regulating hormones at once, then changes in the relative concentrations of these regulators might induce dramatic alterations in cell morphology, physiology and growth. Increased secretions of autocrine growth factors at once, then changes in several growth-regulating hormones at once, then changes in involvements of tonic concentrations of autocrine phenomena and normal control of growth.

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* J. M. Kuhn, personal communication.


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