Perturbations of Iodine Metabolism by Lithium

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ABSTRACT

A kinetic study of the effects of lithium on iodine metabolism in hyperthyroidism is reviewed. The analysis, carried out in collaboration with Mones Berman, disclosed several unexpected findings. In addition to the inhibition of thyroid iodine release predicted by animal studies, an apparent decrease in extrathyroidal iodine disappearance was observed. This was confirmed by a direct study of the metabolic clearance of labeled thyroxine in hyperthyroid subjects. In euthyroid subjects, lithium did not alter thyroxine disappearance. Also unexpectedly, the lithium-induced perturbations did not promptly return to the control state after the serum lithium level had become undetectable. This suggested a delayed release of lithium from extravascular pools, a phenomenon later described in bone. These findings demonstrated the power of kinetic modeling when used as an analytical tool.

In 1968, Schou and associates [1] noted the occurrence of goiter in patients with manic-depressive illness under treatment with lithium salts. Shortly thereafter, Sedvall et al. [2] proposed that this was the result of a blockade of iodine release from the thyroid gland. They found increased retention of thyroid radioiodine together with a rise in the 24-hour uptake, and a decrease in serum protein-bound iodine. This prompted us a few years later to initiate a study of the thyroid effects of lithium in rats [3]. Although acute large doses giving serum lithium levels above 2 mEq per liter, higher than those encountered clinically, interfered with thyroid iodine metabolism at multiple steps, lower doses only inhibited iodine release. This was at an early stage of secretion, as shown by the prevention of TSH-induced endocytosis of follicular colloid [4]. Chronic low-dose lithium, with serum levels between 0.2 and 0.9 mEq per liter, led to iodine-rich goiters resulting from decreased iodine release in conjunction with TSH-driven, enhanced iodine accumulation. The decreased fractional release of an expanded intrathyroidal pool of hormonal iodine explained the maintenance of a euthyroid state. This was also true in patients unless an associated thyroid abnormality (e.g.,

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radiation damage or thyroiditis) prevented the secondary increase in hormone synthesis [5,6].

These observations suggested that lithium might be a valuable agent for the treatment of hyperthyroidism. While sharing the ability of iodide to acutely decrease thyroid hormone secretion, lithium should not expand the intraglandular hormone pool as much as iodide, nor would it interfere with test doses or therapeutic doses of radioiodine. We decided to test this possibility in patients with diffuse toxic goiter. At the same time, we enlisted the help of Mones Berman in designing a study that would extend our knowledge of the effects of lithium in man.

Berman had a long-standing interest in iodine kinetics [7]. Indeed, it was one of the subjects that initiated his involvement in the modeling of biological processes. As the details of iodine metabolism became known, he incorporated them into his steadily expanding SAAM computer program [8], and he saw our lithium study as a way to gain new insights. While we might have obtained our objective in a far simpler fashion, the power of his mathematical approach became evident when it led to the discovery of a hitherto unrecognized effect of lithium on peripheral thyroid hormone metabolism. It also brought to light new aspects about persistent lithium effects, but these remain unresolved because we have not pursued the new directions in which Berman's calculations clearly pointed us. In this review, I want to emphasize these aspects of our collaboration [9,10].

The experimental approach was straightforward. We recruited a group of seven patients with active Graves' disease and injected each with a labeling dose of 200 to 300 μCi of carrier-free Na ^{131}I. During the next 24–36 hr, we made frequent measurements of the ^{131}I content of serum, urine and the thyroid gland. Daily measurements were continued for 7 to 13 days, after which we began lithium treatment. We used lithium carbonate in a loading dose of 600 mg followed by 300 mg 3 to 5 times per day to maintain serum lithium levels of 0.6 to 1.2 mEq/liter. More frequent ^{131}I sampling was done in the initial lithium therapy period. After 1–3 weeks, lithium was discontinued and ^{131}I measurements were continued for another 1–2 weeks. In the serum, protein-bound as well as total ^{131}I was assayed. In four of the eight studies in our seven patients, methimazole, 30 mg every 6 hr, was begun 1–5 days after ^{131}I administration in order to prevent recycling of ^{131}I through the thyroid gland.

The data were analyzed with the digital computer program SAAM/25 described by Berman and Weiss in 1967 [11]. The general model of iodine metabolism, which Berman had developed from the data of several groups of collaborators [12–14], was used, but was modified slightly by incorporating two new thyroidal iodide compartments and one extrathyroidal compartment. This model is illustrated in Figure 1. It consists of an extrathyroidal iodide pool exchanging with thyroidal iodide and receiving ^{131}I from the

metabolism of triiodothyronine (T_3) and thyroxine (T_4) and from two of the new compartments: 17, representing intrathyroidal iodide regeneration, and 19, an extrathyroidal compartment of uncertain identity needed to satisfy early iodide disappearance phases. There are two thyroidal hormonal iodine compartments, 2 and 11, the latter receiving iodine from a delay compartment, 5; the serum T_3 and T_4 compartments receive hormone from all three. Several assumptions made in the calculations are recorded in the legend to Figure 1 in our earlier publication [9] and will not be repeated here. The model does not attempt to resolve the components of intrathyroidal organic iodine, since the iodotyrosines are rapidly converted to iodide. It also does not deal with the extrathyroidal conversion of T_4 to T_3, about which we shall have more to say later. In analyzing the lithium effect on thyroidal secretion, it was not found necessary to introduce different effects on the several intrathyroidal compartments.

The lithium effects in one of the four patients not receiving methimazole are illustrated in Figure 2, with the treatment period shown as a shaded area. In all four patients, serum and urine ^{131}I fell promptly after lithium was begun. The least-squares fits of the data in the pre-lithium period are continued as dashed lines to show the expected results if lithium were not given. The solid lines after lithium were calculated by assuming that the only

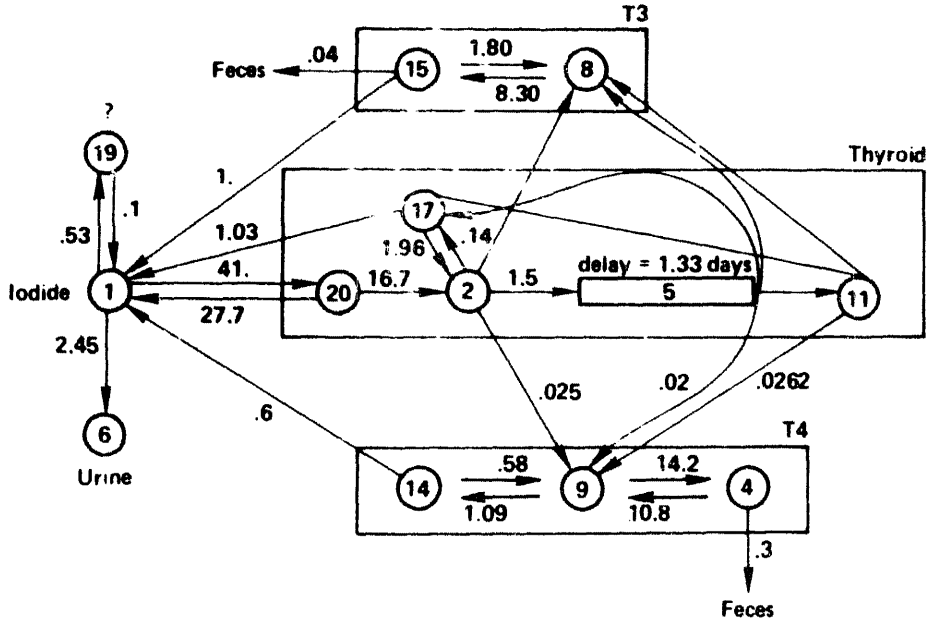

FIG. 1. ^{131}I kinetic model used in the present analysis. The thyroidal and extrathyroidal subsystems are in rectangular boxes, and the compartments are represented by circles. The rate parameters are those used for the hyperthyroid subject shown in Figures 4 and 5. See text for description of changes from previous models. From Temple et al. [9]; see original for further description and assumptions.

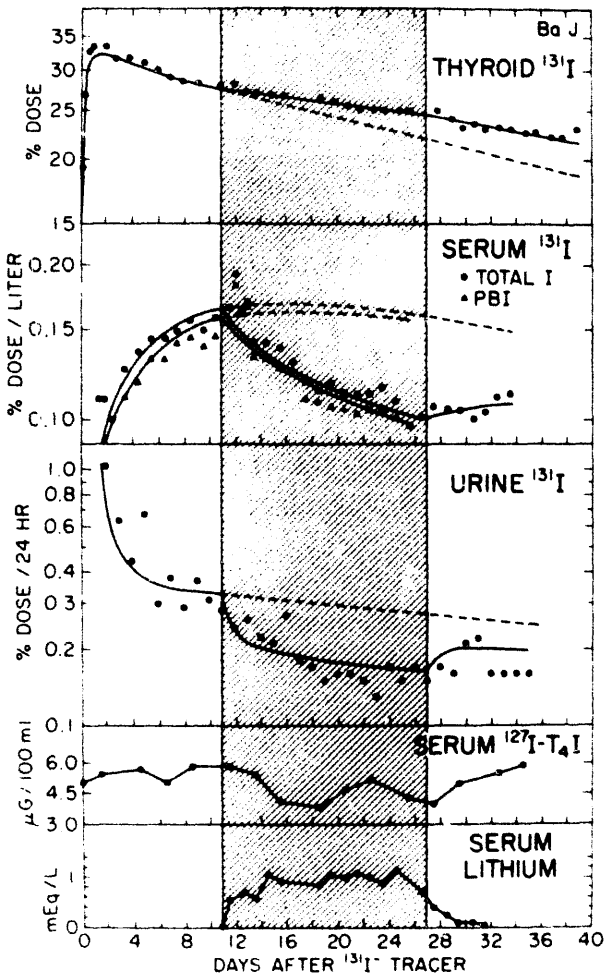

FIG. 2. ^{131}I kinetics in a hyperthyroid patient before, during (shaded area), and after lithium treatment. Filled circles and triangles represent measured data. Solid lines in the three upper panels are computer-generated least-squares solutions, assuming that lithium affected only iodine release. The dashed line is the continuation of the curves fitted to the pre-lithium data. From Temple et al. [9].

effect of lithium was a decrease in total ^{131}I release —i.e., from the three compartments feeding into the extrathyroidal T_4 compartment. As can be seen, the fit to the thyroid, serum, and urine ^{131}I data is quite good. In two of the four patients, however, the data could not be fitted under this simple assumption. The findings in one severely thyrotoxic patient are shown in the left panel of Figure 3, in which the parameters were adjusted to fit the serum data. As can be seen, the thyroid and urine data deviated markedly from the theoretical curves. When, on the other hand, only the thyroid and urine data were fitted in the computer solution (Figure 3, right panel), the calculated serum curve deviated markedly from the data. The too rapidly falling serum curve suggested that lithium might have had a second effect on the rate of

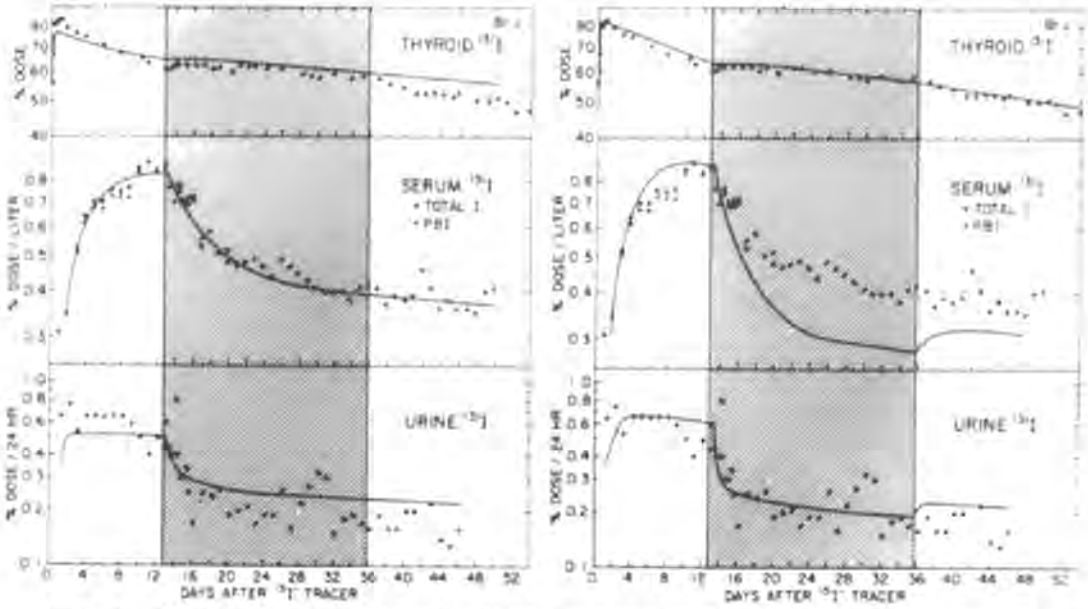

FIG. 3. ^{131}I kinetics in a hyperthyroid patient analyzed as in Figure 2, assuming that lithium affected only iodine release. In the left panel, the parameters were adjusted to fit the serum data. In the right panel, the analysis gave no weight to the serum data. From Temple et al. [9].

serum ^{131}I disappearance. Indeed, when this factor was introduced into the solution, a satisfactory fit was achieved (Figure 4). Since the higher serum ^{131}I levels were accompanied by lower levels in the urine, the most likely cause was a decrease in the pathway of T_4 deiodination, and the fit shown in this figure was obtained by this change alone, aside from the decrease in thyroid ^{131}I secretion.

Four additional studies were done in which methimazole was given, beginning 2 to 4 days after the ^{131}I injection. One of these is shown in Figure 5. In each case, methimazole (MMI) effectively blocked iodide recirculation into the organic iodine pools, leading to an increased rate of ^{131}I loss from the thyroid and an abrupt increase in urine ^{131}I. Lithium, as shown in this case, promptly decreased the loss of ^{131}I from the thyroid. The rate of loss decreased further after several days, perhaps in relation to the increasing serum lithium level. In this patient, it was again necessary to introduce a decrease in serum ^{131}I disappearance rate in order to fit the data during the lithium period.

The results of all eight studies are summarized in Table 1. Lithium caused thyroid ^{131}I release to fall in all cases, but the magnitude of the change was variable, ranging from 30 to 85% of the control value. This magnitude did not correlate with the pretreatment release rate, which ranged from 0.013 to 0.17 d^{-1}. The average decrease, 56%, was somewhat less than the 73% average decrease produced by high doses of iodide in thyrotoxic subjects [15]. An

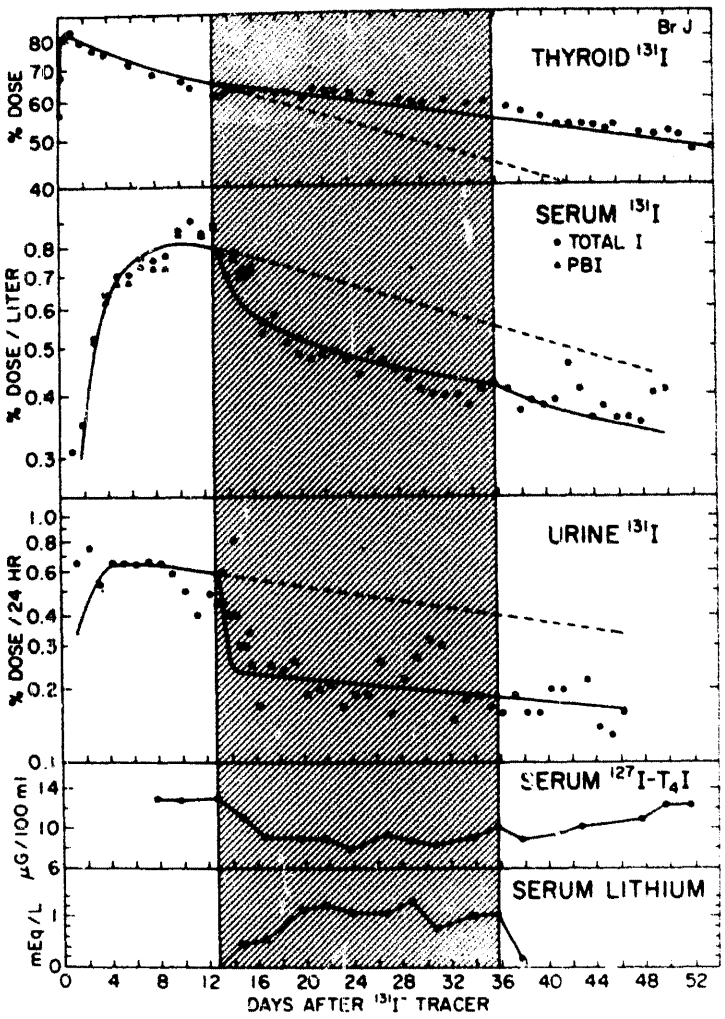

FIG. 4. ^{131}I kinetics in the same patient as in Figure 3. The analysis assumes that lithium affected both iodine release and hormone disappearance. From Temple et al. [9].

additional major effect on the rate of hormonal iodine degradation was predicted in five of the eight studies (Table 1), and it is of interest that the magnitude of this change seems to correlate with the magnitude of the decrease in thyroid iodine release.

As noted earlier, this second lithium effect was quite unexpected. It had not been observed in the animal studies we had done, nor in a study carried out in one patient by R. Bernstein (unpublished). At Berman's urging, however, we investigated the effect of lithium on the disappearance of labeled thyroxine from serum in a separate group of five hyperthyroid and four euthyroid subjects [16]. The results are shown in Table 2. In the hyperthyroid patients, but not in the euthyroid subjects, lithium was found to decrease the disappearance rate by 26 to 45%. Spaulding et al. [17] showed a similar 36% fall in T_4 disappearance in hyperthyroidism, although they also found a 30% fall in euthyroid subjects.

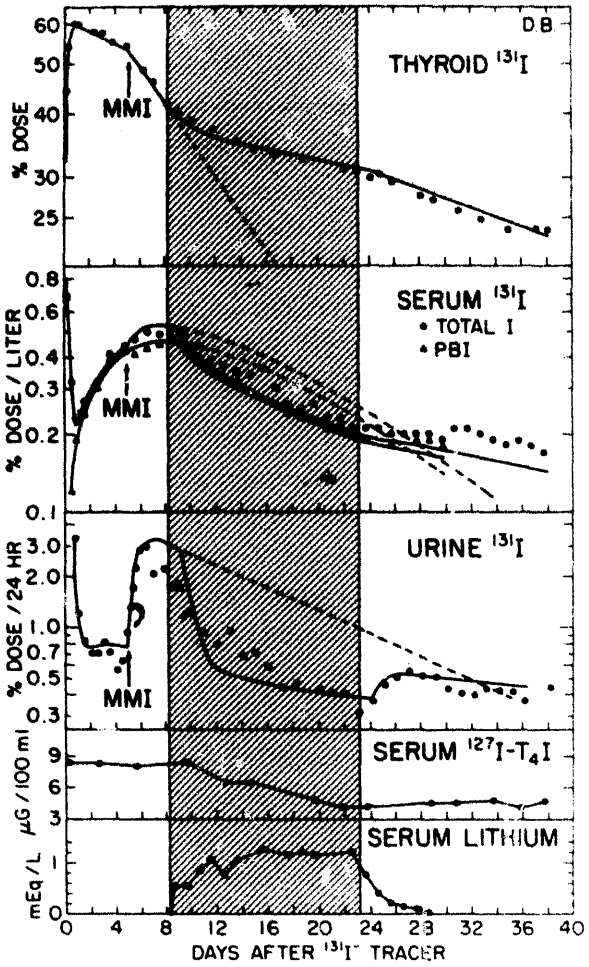

FIG. 5. ^{131}I kinetics in a hyperthyroid patient who was given methimazole, 30 mg every 6 hr, starting on the 5th day after Na^{131}I administration to block iodide organification. The analysis is as in Figure 4. From Temple et al. [9].

The decrease in T_4 disappearance found in these direct studies was somewhat less than we had calculated for most of the patients in the modeling study. However, the direct technique may have given falsely low values because methimazole was not given until several days after the labeled T_4 had been injected. This was to avoid a large fall in the unlabeled serum T_4 level that might otherwise have occurred in response to methimazole therapy. A fall in T_4 level would have caused an increase in fractional T_4 disappearance whereas omission of the recycling blockade would cause an apparent decrease.

Thus, we were able to confirm the prediction made by the kinetic modeling analysis, and to show that the use of lithium in treating hyperthyroidism might be more complex than previously imagined. Since the goal of therapy is to lower the serum hormone level as quickly as possible, this second lithium effect would appear to be counterproductive. On the other hand, a decrease in disappearance of T_4 could be the result of decreased

TABLE 1

Effect of Lithium in Thyrotoxicosis

Patient	Methimazole	Thyroid ^{131}I release rate[a] (%)	$T_3 + T_4$ degradation rate[a] (%)
A	–	−48	−15
B1	–	−63	−70
C	–	−67	−74
D	–	−30	−5
E	+	−60	−40
F	+	−85	−60
G	+	−30	0
B2	+	−65	−50

[a]Percentage change from control value.

monodeiodination of the phenolic ring. Since T_3 is the more active form of the thyroid hormone, this event would be beneficial in lithium therapy. There still have been no definitive studies of this question, although less direct evidence does not seem to indicate an effect of lithium on monodeiodination. In our patients the fall in serum T_3 (19–52%) was slightly greater than the fall in T_4 (15–41%), but this might simply reflect the intrinsically more rapid disappearance of T_3 from blood. Others found a lesser fall of serum T_3 levels either in hyperthyroid [18] or euthyroid [19] subjects. Furthermore, neither of

TABLE 2

Effect of Lithium on T_4 Disappearance

Patient	T_4 disappearance (%/day)		Inhibition by Li^+ (%)
	Pre-Li^+	On Li^+	
Hyperthyroid			
1	17.6	9.7	45
2	16.1	11.7	27
3	15.9	11.8	26
4	18.8	13.6	28
5	26.0	16.3	37
Euthyroid			
1	14.7	13.7	7
2	14.8	13.8	7
3	8.3	8.8	0
4	11.3	11.7	0

these groups found an increase of serum reverse T_3 (3,3′,5′I-T_3), which would be expected if 3′-monodeiodination were blocked; instead, reverse T_3 decreased. Interpretation of these data, however, is complicated by the simultaneous fall in serum T_4 level that occurred. It would be of considerable interest to apply the more complete models of iodine metabolism, such as those recently described by DiStefano et al. [20] and by McGuire and Hays [21], to this interesting question. At the moment we are left with two apparently opposing actions of lithium; nevertheless, the effect on hormone secretion is the most powerful and considerable clinical evidence shows that lithium is indeed beneficial in Graves' disease [9,10,22–24].

The graphs depicting the kinetic studies also show the continuation of the analyses for 1–2 weeks after lithium was stopped. The serum lithium fell to very low levels by 2–4 days, but the rate of ^{131}I secretion and disappearance did not return to normal during the period of study. The findings in all eight studies are summarized in Table 3. In two, the rates actually increased above the pretreatment values, but in the others they remained almost the same as in the lithium period, or reverted only partially. Berman postulated that lithium might have distributed into one or more slowly turning-over compartments and thus continued to exert an effect after most of the drug had left the blood. Only later [6] did information on this question become available. It is now known that lithium enters bone, from which it is discharged very slowly. It is also known that lithium accumulates in the thyroid gland, reaching levels 2–5 times the control. Whether this pool also turns over slowly remains to be seen. Our analyses clearly showed, however, that restoration of prelithium iodine kinetics did not follow promptly the disappearance of lithium from the blood.

TABLE 3

Recovery from the Lithium Effect

	Thyroid ^{131}I Release[a]		$T_3 + T_4$ Degradation[a]	
Patient	On Li^+	Off Li^+	On Li^+	Off Li^+
A	0.52	0.70	0.85	0.85
B1	0.37	0.37	0.30	0.35
C	0.33	0.60	0.25	0.30
D	0.70	1.60	0.95	1.80
E	0.40	0.65	0.60	0.60
F	0.15	0.25	0.40	0.45
G	0.70	—	1.00	—
B2	0.35	1.40	0.50	1.40

[a] Fraction of pre-Rx value.

In this brief presentation, I have tried to demonstrate the kind of fruitful collaboration with Mones Berman that many scientists around the world have enjoyed. In our case, we worked on an old favorite of his, the modeling of iodine metabolism. The beauty of this study was that it showed that the kinetic analysis of a biological phenomenon is not merely a refined way of treating data so as to quantify rates and pools. Rather, it is an analytical method that starts with the definition of known processes and can then be used to reveal deficiencies in our understanding. This can lead to an advancement in our knowledge. This was a central theme in Mones Berman's work and still needs to be impressed on scientists such as ourselves.

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