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Lithium in Scalp Hair of Adults, Students, and Violent Criminals

Effects of Supplementation and Evidence for Interactions of Lithium with Vitamin B_{12} and with Other Trace Elements

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ABSTRACT

The lithium content of human hair shows an approximately linear response to extradietary lithium supplementation at dosage levels of up to 2000 μg/d. From the mean hair lithium concentration of 0.063 μg/g in 2648 predominantly American adults, and the reference hair lithium concentrations determined in the present study, the mean lithium intakes were calculated to be 730 μg/d. Hair lithium concentrations were extremely low in nearly 20% of the American samples, and in samples collected in Munich, Germany and Vienna, Austria. Hair lithium levels are low in certain pathological conditions, e.g., heart disease, in learning-disabled subjects, and in incarcerated violent criminals. The highest levels were observed in samples of a lithium-treated psychiatric patient.

A statistically highly significant direct association was observed between the hair lithium and cobalt concentrations, which suggests a role of lithium in the transport and distribution of vitamin B_{12}. Interactions of lithium with other trace elements are also discussed.

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Index Entries: Lithium, lithium supplementation, effect on scalp hair lithium levels, association of hair lithium with hair cobalt levels; Vitamin B_{12}—lithium interactions; Violent subjects, learning disabled subjects.

INTRODUCTION

Lithium (Li) is a newly discovered essential trace element whose physiological roles are still largely unexplored. Animal experiments have demonstrated that a deficiency of this alkali metal ion is associated with reproductive failure, diminished growth, shortened life expectancy, and other abnormalities (*1,2*).

Human Li deficiency syndromes have not yet been identified. However, inverse associations between mental hospital admissions (*3,4*), suicides, violent crimes, and the concentrations of lithium in drinking water (*5,6*) suggest that Li may have important functions. At present, the human Li requirements are unknown. Because Li is rapidly excreted, assessments of lithium status would require multiple determinations of Li in serum, blood, or urine. To obtain information on the long-term average Li intakes from a single measurement, hair or toenails would appear to be more appropriate. Human hair was explored in the present study, since the utility of hair as an indicating matrix of organ Li status has been demonstrated in animal experiments (*7*).

In the present article, we will show that the Li concentrations in human hair increase in response to Li supplementation. In addition, we report on hair lithium levels from different locations in the USA, from subjects in several other countries, from incarcerated violent criminals, and from hospitalized heart patients. Associations of Li with other elements and with vitamin B_{12} will also be discussed.

MATERIALS AND METHODS

Lithium Supplementation Experiments

The effect of supplementary lithium on hair Li levels was studied by self-supplementation experiments during which the three subjects ingested at first Li-yeast supplements corresponding to 2000 μg of Li/d for 6 mo. Supplementation was then stopped for 2 mo. It was subsequently resumed at the level of 1000 μg/d for the next 6 mo. The lithium was ingested in the form of lithium-enriched Brewer's yeast obtained from Cell-Life Corp., San Diego, CA; the Li content of the yeast was checked by independent analysis. The average age and weights of the experimental subjects, all males, were 49 ± 7 yr and 179 ± 6 lb, respectively.

Analysis

Hair samples of the subjects were obtained by cutting newly grown hair from the nape of the neck using stainless-steel scissors. Lithium determinations were performed by Doctor's Data of Chicago, IL, using inductively coupled plasma spectroscopy (ICPS). Prior to wet-ashing with $HNO_3/HClO_4$, hair samples were washed four times with Triton X-100 detergent solution, rinsed once with acetone, three times with water, and twice more with acetone.

Hair Samples

Hair samples from randomly selected adults were collected from the cities of San Diego (CA), Munich (Germany), Vienna (Austria), Tokyo (Japan), Tijuana, and Culiacan (Mexico), and were analyzed for Li by the method described above. Li and other trace element levels in 2648 previously analyzed samples, mainly from US residents, from incarcerated violent criminals of institutions in California, Florida, and Oregon were kindly provided prior to publication (*see* ref. *17*) by E. Hodges, Tustin, C the hair analysis data from hospitalized heart patients were furnished by B. L. Smith from Doctor's Data, Chicago. Hair samples from a female manic patient on lithium therapy were provided by a local psychiatrist.

RESULTS

Lithium Supplementation Studies

Figure 1 shows the changes of the hair Li concentrations in subjects 1–3 in response to Li supplementation. Figure 2 reveals that the dose–response relationship is approximately linear within the dosage range investigated. The least-squares fitted line is:

$$[Li_{intake}] = 11.6[Li_{Hair}] - 0.43 \quad (1)$$

when Li_{intake} is measured in mg/d and Li_{Hair} in μg/g. The mean hair Li concentration in three samples of hair collected at monthly intervals of a female manic-depressive patient on lithium therapy was 0.33 ± 0.10 μg/g.

Changes in the concentrations of elements in hair in response to Li supplementation are shown Table 1 and in Fig. 3. It may be seen that hair Al, V, Co, Pb, and As concentrations increased during the period of Li supplementation. To establish the primary origin of hair Co, separate duplicate Co determinations in hair samples of subject #1 were per- ned 8 and 4 wk before, and 4, 8, and 12 wk after obtaining an im njection of 5000 μg vitamin B_{12}. The initial average hair Co concentration of 0.10 ± 0.04 μg/g prior to B_{12} administration reached a maximum value

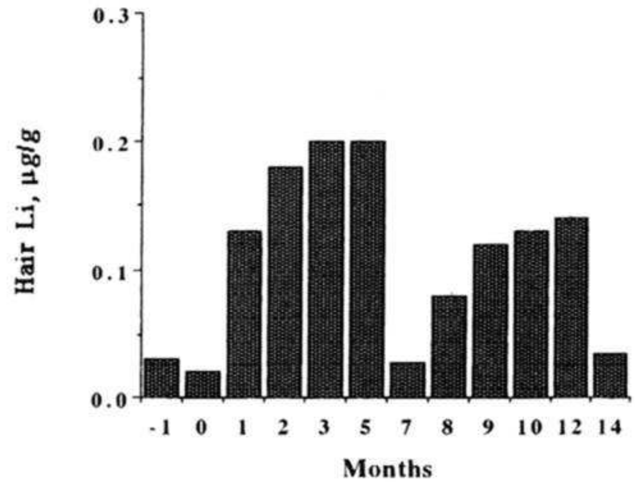

Fig. 1. Changes of hair lithium concentrations of the experimental subjects during supplementation first with 2000 μg/d (mo 0–5), followed by 1000 μg/d (mo 7–12).

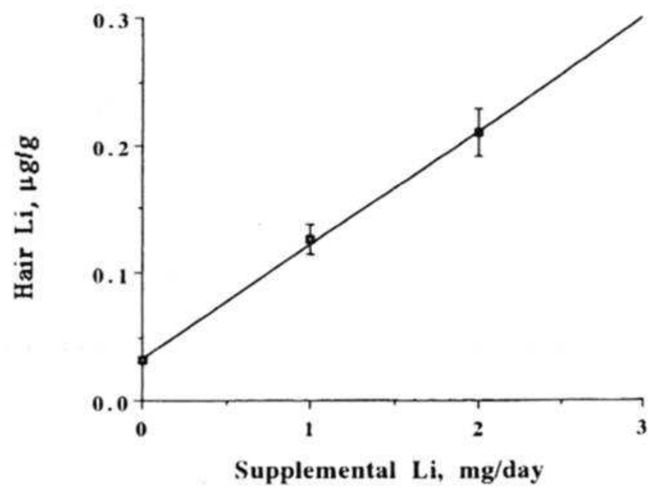

Fig. 2. Relationship between hair lithium concentrations after 3 mo of supplementation at 1000 and 2000 μg/d.

of 0.35 ± 0.002 μg/g 4 wk after B_{12} administration, and declined to 0.25 ± 0.002 and 0.12 ± 0.001 μg/g after 8 and 12 wk, respectively.

The Mn concentrations dropped in two subjects during Li supplementation, from 0.59 to 0.11 μg/g and 0.71 to 0.17 μg/g. In one subject, the presupplementation Mn levels were low (0.06 ± 0.02 μg/g), and remained unchanged during and after Li supplementation.

Table 1
Average Element Concentrations (μg/g) in Scalp Hair Before and During Lithium Supplementation (2 mg Li/D)[a]

Element	Presuppl.		Suppl.	
Ca	220	(85)	229	(15)
Mg	27	(7)	20	(9)
Na	53	(38)	45	(11)
K	25	(13)	35	(17)
Cu	6.5	(0.7)	7.5	(0.8)
Zn	121	(15)	118	(10)
Fe	6.5	(2.0)	8.5	(1.5)
Mn	0.63	(0.08)	0.14	(0.07)[b]
Cr	0.41	(0.08)	0.53	(0.09)
Co	0.07	(0.03)	0.15	(0.03)[b]
Li	0.037	(0.01)	0.20	(0.01)[c]
Mo	0.90	(0.15)	0.95	(0.14)
P	102	(12)	111	(15)
Se	0.56	(.16)	0.58	(0.09)
Si	3	(1)	3.5	(0.8)
V	0.06	(0.02)	0.26	(0.03)
Sr	0.6	(0.2)	0.7	(0.2)
Ba	0.25	(0.09)	0.2	(0.)
B	4.5	(1.1)	5.3	(0.6)
Pb	1.5	(0.6)	4.0	(0.7)[b]
As	0.6	(0.2)	1.3	(0.7)[b]
Hg	0.3	(0.1)	0.3	(0.1)
Cd	0.1	(0.1)	0.3	(0.1)
Al	1.6	(0.3)	4.0	(0.5)[c]
Ni	0.6	(0.3)	0.7	(0.3)
Be	0.02	(0.01)	0.02	(0.01)

[a] $N = 3$, except for Mn, where $N = 2$.
[b] $P = 0.05$.
[c] $P = 0.01$.

Results for Adults, Students, and Violent Criminals

The frequency of distribution of hair Li as obtained from the data of 2648 subjects is shown in Fig. 4. The Li content of 65% of the samples ranged from 0.04 to 0.14 μg/g, 16.6% contained more than 0.14 μg/g, and the remaining 18.4% of the samples contained < 0.04 μg/g.

The concentrations of Li in hair of residents from cities in several states and of other subjects are shown in Table 2. The highest mean Li levels were observed in hair of students from Tijuana, Mexico, and the lowest in samples of adults from Vienna, Austria and Munich, Germany.

The mean hair Li, Mn, Ca, and Mg levels of violent criminal offenders from a California prison and of nonincarcerated controls are given in Table 3. Table 4 compares the Li, Mn, Ca, and Mg concentrations in hair of inmates of a California prison with those of hospitalized

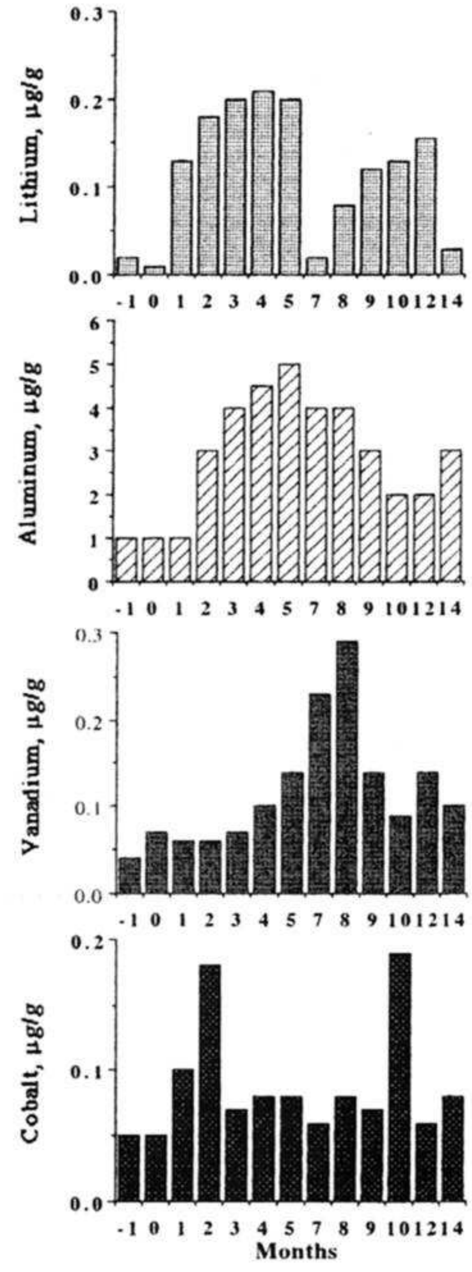

Fig. 3. Changes of hair Li, Al, V, and Co levels during lithium supplementation.

heart patients. Figure 5 shows the Li and Mn distribution in hair of violent criminal offenders and of age-matched controls. Figure 6 indicates the association of Li and Co levels in hair samples of adults from different countries. Figure 7 reveals the Li–Co relationships in two groups of Tijuana students of a technical college; A = top students, B =

Table 2
Lithium Levels in Scalp Hair from Residents of Several Cities

City, Country	*N*	Li, µg/g	SD
Vienna (Austria)	20	0.030	0.025
Munich (Germany)	18	0.035	0.033
Tokyo (Japan)	20	0.070	0.033
Galveston (Texas)	25	0.080	0.059
Culiacan (Mexico)	21	0.081	0.080
Kopenhagen (Denmark)	20	0.087	0.021
Stockholm (Sweden)	10	0.094	0.028
Tijuana (Mexico)	60	0.128	0.087

Table 3
Lithium Concentration in Scalp Hair from Normal Males and Male Violent Criminal Offenders from Prisons in California, Oregon, and Florida

	N	Li, µg/g	SD
Controls (California)	82	0.099	0.126
Violent offenders (California)	49	0.028	0.029
Prisoners (Florida)	48	0.032	0.031
Prisoners (Oregon)	31	0.051	0.052

Table 4
Concentrations of Li, Mn, Ca, and Mg in Scalp Hair of California Healthy Subjects, California Violent Offenders, and of Heart Patients

Element	Controls $N = 72$	Prisoners $N = 49$	Heart patients $N = 42$
Li (µg/g)	$0.099 \pm 0.124^{a,b}$	0.028 ± 0.028	0.023 ± 0.024
Mn (µg/g)	$0.316 \pm 0.246^{a,b}$	0.721 ± 0.821	0.226 ± 0.249
Ca (mg/g)	1.099 ± 0.646	1.248 ± 0.711	$0.317 \pm 0.238^{a,b}$
Mg (mg/g)	0.089 ± 0.054	0.057 ± 0.035	$0.028 \pm 0.025^{a,b}$

$^{a,b}P < 0.005$ rel. to data in other columns (Student's *t*-test).

average students. Figure 8 shows the Li-Co relationship in California prisoners characterized as "very violent."

DISCUSSION

Effects of Lithium Supplementation on Hair Lithium Concentrations

Figure 1 shows that Li at supplemental intakes of 1000 and 2000 µg/d causes a dose-dependent increase in hair Li levels. At the dosages chosen, hair Li concentrations noticeably increased after 4 wk of supplementation and became stationary after 3 mo of supplementation at this range. On cessation of supplementation, hair Li values declined to near

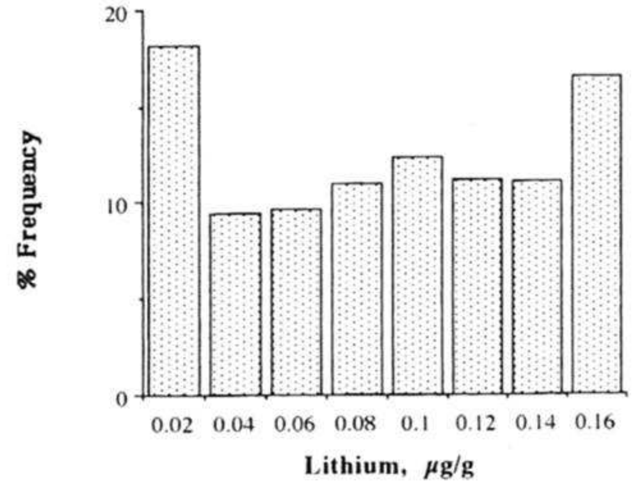

Fig. 4. Frequency distribution of hair lithium concentrations in 2648 human hair samples (in % of total).

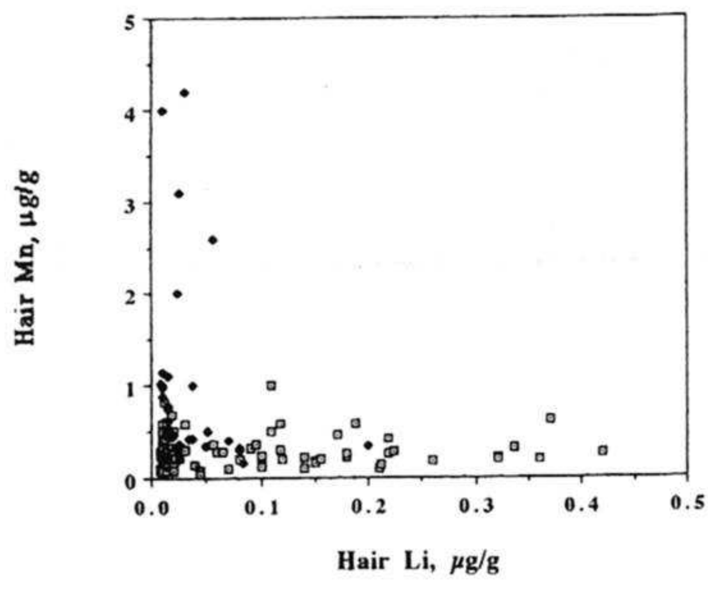

Fig. 5. Distribution of hair Li and Mn concentrations in normal subjects (empty squares) and in violent offenders (full squares).

presupplementation values within 2 mo. Figure 2 reveals a linear relationship between hair Li and supplemental Li within the dosage range studied. This relationship does not extend to therapeutic doses of lithium carbonate. In one psychiatric patient whose daily dosage of lithium carbonate was 600 mg, hair Li levels in three samples taken at monthly intervals ranged from 0.20–0.39 μg/g.

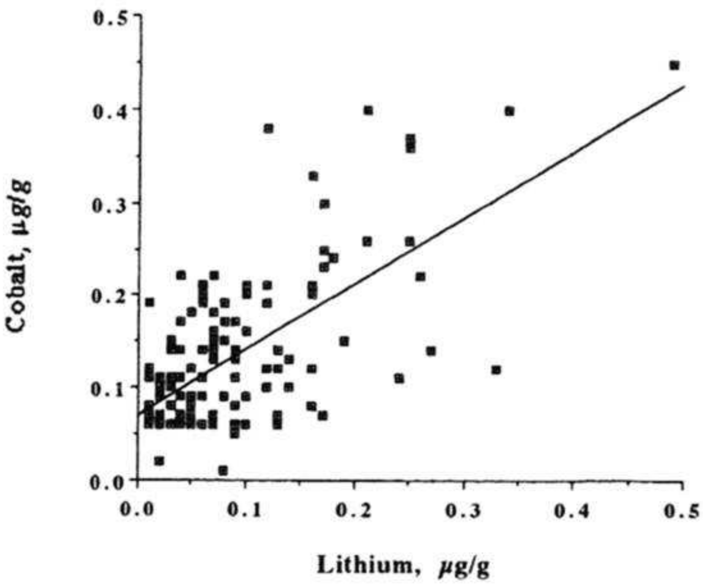

Fig. 6. Correlation of hair Li and Co concentrations in human subjects.

For nutritional Li intakes within the range of the present study, the approximate average long-term daily Li intakes in mg/d of an adult can be calculated by multiplication of the hair Li concentrations (in µg/g) with the factor 11.6. From the intercept of the least-squares fitted line in Fig. 2, the apparent dietary Li intake of subjects 1–3 was calculated to 500 µg/d, which is less than the average intake of 730 µg/d calculated for the 2648 subjects and below the intake range of 650–3100 µg/d estimated by the US Environmental Protection Agency for a 70-kg adult (*8*); the latter values represent the total Li intakes from foods, not all of which is bioavailable. Hair Li levels in a significant percentage of subjects were essentially at the detection limit. In these cases, Li intakes are probably extremely low.

The hair Li concentrations of subjects 1–3 were within the range of hair Li values of normal subjects observed by other authors. Creason et al. (*9*), for example, reported a median hair Li concentration of 0.056 µg/g and a range from 0.009–0.228 µg/g (N = 206) in adults from the New York metropolitan area, which would correspond to a median Li intake of 650 µg/d and a range of 100–2,645 µg/d. The geometric mean for children (ages 0–15) was 0.044 µg/g, with a range of 0.009–0.30 µg/g (N = 277). Hair Li levels were sex-dependent (slightly higher values in females than males). In children but not in adults, external contamination by housedust was an additional, though minor contributing factor.

Table 2 shows that the mean hair Li values in the samples from Vienna, Austria or Munich, Germany, were lower than those from California or Japan. This is in accord with Anke et al.'s reported Li intakes of

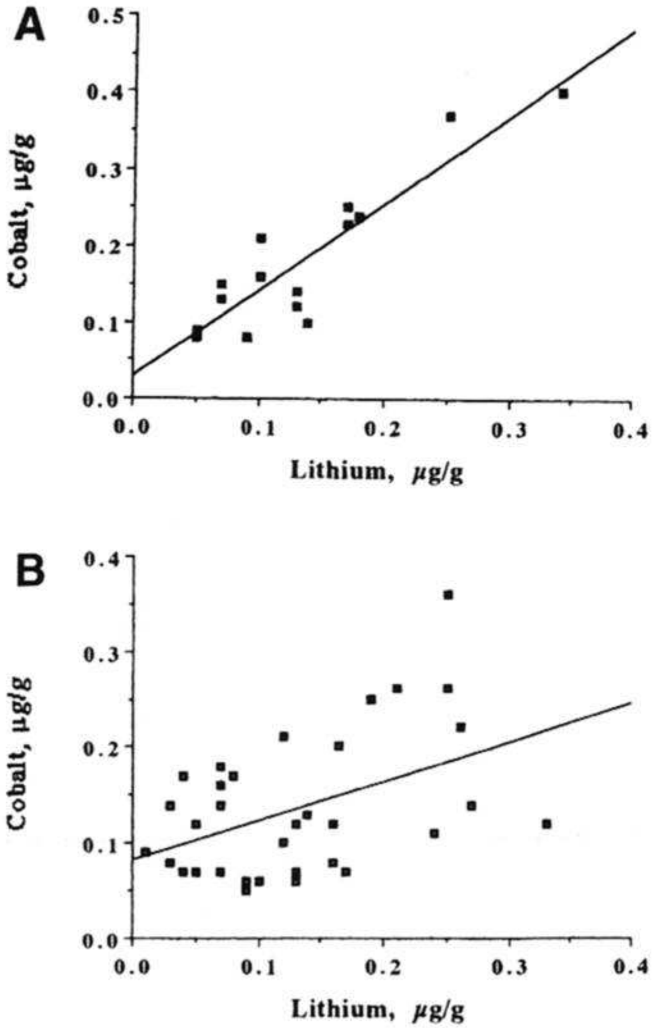

Fig. 7. Correlation of hair Li and Co concentrations in Tijuana students. A: Students in very good academic standing: [Co] = 1.140[Li] + 0.0282, r^2 = 0.811, N = 15. B: Average students, [Co] = 0.405[Li] + 0.084, r^2 = 0.205 (P = 0.05).

men and women in four East German cities (*1*), which ranged from 182 ± 121 to 713 ± 532 µg/d. Since the Li contents of foods consumed were rather similar, the Li intake variations must have been primarily caused by different Li contents of the beverages consumed. The drinking water and beverages, such as soft drinks and beer, can be major sources of Li, although their Li content is highly variable; for Coke and beer, Anke (*1*) lists Li contents of 201 ± 162 and 149 ± 60 µg/L, respectively. Hair Li levels may also be influenced by variations of Li retention, which in turn

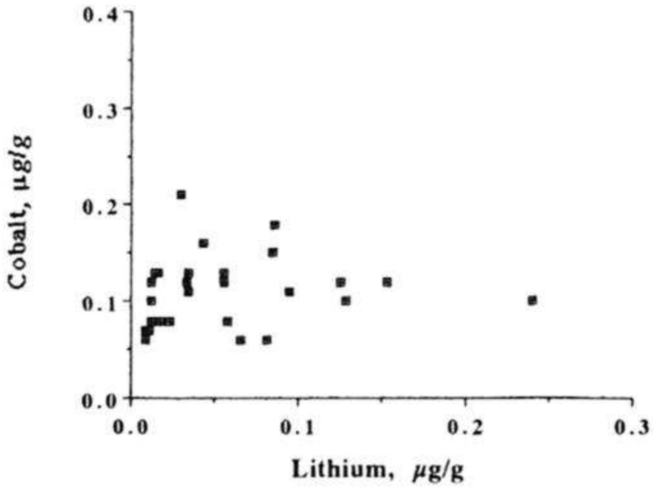

Fig. 8. Correlation of hair Li and Co concentrations in hair of California prisoners.

should depend on dietary factors, total fluid and salt intake, heart, kidney, and intestinal function, physical activity, and endocrine parameters. Tables 3 and 4 show that the hair Li levels of incarcerated violent offenders are lower than those of controls; the possible reasons for this will be discussed below. Table 4 also indicates that the hair Li levels of heart patients are lower than those of healthy controls. Other workers have shown that Li concentrations are lower in infarcted than in noninfarcted human hearts (*22*), but cautioned that this is not indicative of a causal relationship. Similarly, the lower Li concentrations in hair of heart disease patients are more likely a consequence of the disease, i.e., edema, especially since the concentrations of several other elements, e.g., Mn, Ca, and Mg, are also lowered proportionately. In a previous retrospective study (*23*), the risk of myocardial infarction was found to be associated with a pattern of deceased hair Mg, Sr, Ba, and Cu levels with an increased Ca/Mg ratio.

Interactive Effects of Lithium with Other Elements

Lithium influences the physiological transport and distribution of other minerals and trace elements, which has been suggested to account for some of the therapeutic effects of Li. The first element mentioned in this context was bromide, which was shown to be elevated in serum of patients receiving Li treatment (*10,11*).

Campbell et al. (*12*) found that the hair of patients on lithium contains more iodine (I), but less fluorine (F). The elevation of I suggests an interaction between Li and I that may be associated with the thyroidsuppressing action of Li (*13*). The depression of F could be indicative of an interaction with Li, resulting in a diminished uptake of F or the deposition of Li and F in a storage organ.

Vanadium, Aluminum, Lead, and Arsenic

Table 1 reveals that hair V, Al, Pb, and As concentrations increased intermittently during Li supplementation. Cobalt also increased, as discussed separately below.

Campbell et al. (*12*) previously observed that the concentrations of V and Al as well as of As, Cd, and of a number of other elements were elevated in the hair of Li-treated patients as compared to the controls. These workers also found lower serum concentrations of V in Li-treated patients, whenever Al was increased, suggesting that Li affects the distribution, retention, or elimination of these elements and mobilizes them from body stores, such as the bones.

The diminution of serum V levels in response to Li therapy was cited in support of the hypothesis (*13*) that the therapeutic activity of Li in the treatment of depression is owing to its ability to reduce vanadium levels; elevated serum and blood vanadium concentrations have been observed in some depressed patients, which returned to normal with recovery (*14,15*). Lithium was suggested on the biochemical level to act by decreasing vandate-induced inhibition of NaK-adenosine triphosphatase (ATPase) (*16*). Because of its small ionic radius and positive charge, Li could be envisaged to alter the distribution of other elements; these effects clearly warrant further attention in relation to the mechanism of therapeutic action of Li.

Manganese

The observed decline of the hair Mn concentrations during Li supplementation (*see* Table 1) compares well with the previously reported lower hair Mn concentrations of patients receiving Li therapy (*12*).

Manganese levels have been shown to be elevated in hair of violent criminal offenders (*17*). Table 4 shows that the violent offenders of the present study also have significantly lower hair Li levels than age-matched, nonincarcerated controls. As may be seen in Fig. 4, the distributions of these elements are different in the two groups: The Mn concentrations in the samples of the controls were generally low, the Li concentrations were higher and distributed over a wider range.

Elevations of hair Mn may have numerous causes, which will not be discussed here. However, our observations suggest they may in some cases be associated with low Li intakes. Hence, a causal relationship between elevated hair Mn and violent behavior may not exist. In addition, manganese may be a marker of violent behavior only in some subjects, and different markers may apply for others. Cromwell et al. (*18*) performed a discriminant analysis to determine which elements in hair best disciminated between violent and nonviolent subjects. The most important parameters were found to be the Zn/Cu ratio, followed by Cu and K, and the combination of and interaction among levels of Mg, Si, Cu, Li, Fe, Zn, and Cr. The Cu/Fe and Zn/Cu ratios accounted for 48% variation between the two groups. In their study population, Mn contributed only slightly to the total discriminant function. However, in other studies, Walsh (*19,20*) found that the most violent subjects had elevated hair Cu, Ca, Cd, Pb, and Fe, and depressed Na, K, Zn, Li, and Co; the least violent subjects had elevated hair Ca and Mg, and depressed Zn, Cu, Mn, Na, and K. Furthermore, Pihl et al. (*21*) noted uniformly negative correlations between teachers' rating and elevated hair Mn, and positive associations of the ratings with hair Li levels in Canadian learning-disabled students.

Interactions Between Lithium and Cobalt (Vitamin B_{12})

The observed intermittent increase in hair Co concentrations during Li supplementation in Fig. 3 prompted us to correlate hair Li and Co concentrations in various sets of samples. Statistically highly significant direct associations were observed that were essentially independent of the geographical origin of the samples, allowing American, German, Japanese, and Mexican samples to be pooled, producing Eq. 2

$$[Co] = 1.1015[Li] + 0.0598 \qquad (2)$$

of the least-squares fitted line if Co and Li levels were in units of μg/g, for which $r^2 = 0.577$ with data from 104 samples, $P < 0.0001$; *see* Fig. 6. With some sample sets, the slope of the least-squares fitted lines differed from the slope given above, and the r^2 value was lower. For example, whereas the Li and Co values of hair collected from the top 15 Mexican students essentially coincided with the least-squares fitted line given above, subsequently collected data for 43 academically average students of lower socioeconomic status produced an equation with a significantly smaller slope (Eq. 3)

$$[Co] = 0.405[Li] + 0.084 \qquad (3)$$

with $r^2 = 0.205$ ($P = 0.05$); *see* Fig. 7. To account for the association between Li and Co, the origin of cobalt in human hair must first be discussed. In the absence of external contamination, it is primarily owing to, or derived from, vitamin B_{12}, as evidenced from the observed significant increase of hair Co in response to an injection of 5000 μg of vitamin B_{12} (*see* Results section). Accordingly, the direct association of hair Co with hair Li is indicative of a role of Li in vitamin B_{12} uptake or transport. Such a role was first suggested by studies of Tisman et al. (*24*). These authors found that Li ingestion was associated with elevated levels of unsaturated B_{12} binding capacity. Subsequently, Coleman and Herbert showed that lithium stimulated the release of both B_{12} and folate binding factors from granulocytes (*25*). In vitro studies with L-1210 cells (*26*) revealed that LiCl added to the culture medium significantly increases B_{12} transport into these cells. This could be true for hair follicles, as well and K, and the combination of and interaction among levels of Mg, Si, Cu, Li, Fe, Zn, and Cr. The Cu/Fe and Zn/Cu ratios accounted for 48% variation between the two groups. In their study population, Mn contributed only slightly to the total discriminant function. However, in other studies, Walsh (*19,20*) found that the most violent subjects had elevated hair Cu, Ca, Cd, Pb, and Fe, and depressed Na, K, Zn, Li, and Co; the least violent subjects had elevated hair Ca and Mg, and depressed Zn, Cu, Mn, Na, and K. Furthermore, Pihl et al. (*21*) noted uniformly negative correlations between teachers' rating and elevated hair Mn, and positive associations of the ratings with hair Li levels in Canadian learning-disabled students.

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Variations of the dietary lithium intakes could affect serum B_{12} levels in a manner depending on the amount of B_{12}, which can be mobilized, and the rate of cellular B_{12} uptake. This could account for the intermittent increases of hair Co levels as observed during Li supplementation (*see* Fig. 4).

The effects of Li on vitamin B_{12} transport could be magnified in patients receiving therapeutic doses of Li, initially causing increases, but on prolonged treatment, decreases of serum B_{12} levels. This could explain why Campbell et. al.'s Li-treated patients had significantly lower serum Co levels compared to the controls (*12*), whereas those of Tisman et al. (*24*) showed elevated B_{12} levels.

Although the concentrations of Li and Co in hair were found to be proportional in the majority of cases, in some samples, Co concentrations were low at high hair Li levels, suggesting that, in these cases, B_{12} stores were low. Where both Li and Co are low, B_{12} stores could either be low or adequate, but B_{12} utilization or transport could be impaired because of Li deficiency. In these cases, Li supplementation should produce an increase of hair Co concentration. Finally, high hair Co coupled with low hair Li in the absence of external contamination or B_{12} therapy could indicate a mobilization of B_{12} owing to a pathological process.

These findings are of potential significance for the behavioral sciences and psychiatry. We have already mentioned that violent criminals, according to Walsh (*19,20*), exhibited depressed hair Li and Co levels. Hair Li and Co levels were also depressed in the California prisoners of our study characterized as "very violent," and this group of samples was the only one not exhibiting a statistically significant Li–Co relationship (*see* Fig. 8). Since violent behavior and learning disability are interconnected, it is significant that Pihl et al., in their study of Canadian learning-disabled students (*21*), found hair Co levels to be positively correlated with teachers' ratings on the Myklebust pupil rating scale to almost the same degree as those with the hair Li levels. The ratings included: total score, auditory comprehension, spoken language, orientation, behavior, and motor functions. Conceivably, in these cases, low Li intakes were coupled with marginal B_{12} body stores. The same may also have been the case in the academically marginal students of Fig. 7, wherein increases of dietary Li were associated with smaller increases of hair Co levels possibly owing to malnutrition.

The profound effects of vitamin B_{12} deficiency on mood and behavior are well known. In previous studies with pernicious anemia patients, the following psychiatric manifestations were reported (*27*) to abate with vitamin B_{12} therapy (emphasis ours): Confusion, hallucinations, delusions, disorientation, confabulation, anxiety, restlessness, fatigue, depression, irritability, sleepiness, psychosis, introspection, stupor, slow cerebration, decreased memory, acute delirium, mania, apathy, lack of energy, weakness, subacute organic reactions, *violent behavior*, self-pity, flight of ideas, negativism, acute paranoid states. These symptoms may occur in the absence of hematological signs of B_{12} deficiency.

It thus would seem that certain behavioral defects, depression, and forms of learning disability could be caused by, or aggravated by low nutritional Li intakes coupled with marginal deficiencies of B_{12}, as well as folic acid, whose transport is also modulated by Li (*28*).

NOTE

Upon completion of this work, T. Ono and Wada (*29*) found that rats on a Li-deficient diet (6.6 ng Li/g diet) showed significantly suppressed lever-press avoidance behavior as compared to animals on a Li-supplemented diet (110 ng Li/g diet). The behavior of the Li-deficient animals normalized on Li supplementation. This result provides the first direct evidence from animal studies for a beneficial effect of Li at nutritional levels on behavior.

In addition, Arnold et al. (*30*) reported that the mature milk of Li-deficient lactating goats contained twice as much manganese than the milk of Li-adequate controls, demonstrating an effect of Li deficiency on Mn metabolism.

REFERENCES

1. M. Anke, W. Arnhold, B. Groppel, and U. Krause, in *Lithium in Biology and Medicine*, G. N. Schrauzer and K. -F. Klippel, eds., VCH Publishers, Weinheim, New York, Basel, Cambridge, 1991, pp. 149–167, and references cited therein.
2. M. Anke, B. Groppel, H. Kronemann, and M. Gruen, *4th Trace Element Symposium*, K. Marx University, Leipzig, 1983, p. 5865.
3. E.B. Dawson, in *Lithium in Biology and Medicine*, G. N. Schrauzer and K. F. Klippel, eds., VCH Publishers Weinheim, New York, Basel, Cambridge, 1991, pp. 171–183.
4. E. B. Dawson, T. D. Moore, and W. J. McGanity, *Dis. Nerv. Syst.* **31**, 1 (1970); ibid., **33,** 546 (1972).
5. G. N. Schrauzer and K. P. Shrestha, in *Lithium in Biology and Medicine*, G.N. Schrauzer and K. -F. Klippel, eds., VCH Publishers Weinheim, New York, Basel, Cambridge, 1991, pp. 191–203.
6. G. N. Schrauzer and K. P. Shrestha, *Biol. Trace El. Res.* **25,** 105 (1990).
7. H. Kronemann, M. Anke, B. Groppel, and E. Riedel, *4th Trace Element Symposium*, K. Marx University, Leipzig, 1983, p. 8589.
8. D. S. Saunders, Letter: United States Environmental Protection Agency, Office of Pesticide Programs (1985).
9. J. P. Creason, T. A. Hinners, J. E. Bumgarner, and C. Pinkerton, *Clin. Chem.* **21**, 603 (1975).

10. C. A. Campbell, M. Peet, and N. I. Ward, *Biol. Psychiatry* **24,** 775 (1988).
11. C. R. Handorf, J. H. Coleman, and W. N. Rawls, *J. Clin. Psychiatry* **46,** 9 (1985).
12. C. A. Campbell, N. I. Ward, and M. J. Peet, *Affect. Dis.* **11,** 161 (1986).
13. R. R. Fieve and E. D. Peslow, in *Lithium: Current Applications in Science, Medicine and Technology*, J. Wiley & Sons, New York, 1985.
14. G. J. Naylor, H. H. W. Smith, D. Bryce-Smith and N. I. Ward, *Psychol. Med.* **14,** 767–772 (1984).
15. G. J. Naylor and A. H. W. Smith, *Psychol. Med.* **11,** 249 (1981).
16. G. J. Naylor, D. A. T. Dick, B. B. Johnston, S. E. Hopwood, E. G. Dick, A. H. W. Smith, and D. Kay, *Lancet* **ii,** 1175, 1176 (1981).
17. L. A. Gottschalk, T. Rebello, M. S. Buchsbaum, H. G. Tucker, and E. L. Hodges, *Comprehensive Psychiatry* **32(3),** 1–9 (1991).
18. P. E. Cromwell, B. R. Abadie, J. T. Stephens and M. Kyler, *Psychol. Reports* **64,** 259 (1989).
19. W. J. Walsh, 37th Ann. Meeting of the American Society for Criminology, San Diego, CA, 1985.
20. W. J. Walsh, Chemical imbalance and criminal violence: Results of two controlled studies of California institutions. Unpublished manuscript, Health Res. Institute, Chicago, cited in ref. 18.
21. R. O. Pihl, H. Drake and F. Vrana, in A. C. Brown and R.G. Crounse, eds., *Hair, Trace Elements and Human Illness*, Praeger Scientific, New York, 1980, pp. 128–143.
22. W. Baumann, G. Stadie and M. Anke, *4th Trace Element Symposium*, K. Marx University, Leipzig, 1983, pp. 180–185.
23. B. L. Smith, *Trace El. in Medicine* **4(3),** 131–133 (1987).
24. G. Tisman, V. Herbert and S. Rosenblatt, *Br. J. Hematol.* **23,** 767 (1973).
25. V. Herbert and N. Coleman, in *Lithium Effects on Granulopoiesis and Immune Function*, A. H. Rossof and W. A. Robinson, eds., Plenum, New York, 1980, pp. 61–78.
26. L. Vanyo, Th. Vu, M. Ramos, J. Amin, S. Conners, R. Bateman and G. Tisman, in *Lithium in Biology and Medicine*, G. N. Schrauzer and K. -F. Klippel, eds., VCH Publishers, Weinheim, New York, Basel, Cambridge, 1991, pp. 17–30.
27. M. Hector and J. R. Burton, *J. Amer. Geriatr. Soc.* **36(12),** 1105 (1988).
28. M. T. Abou-Saleh, and A. Coppen, *Acta Psychiatr. Scand.* **80,** 78 (1989).
29. T. Ono and O. Wada, *Biomed. Res. Trace El.* (Japan Society for Biomedical Research on Trace Elements) **2(2),** 264 (1991).
30. W. Arnold, M. Anke, and U. Kraeuter, "Mengen u. Spurenelemente", Proceedings of the 11.Meeting in Leipzig, Dec. 12, 13, 1991, University of Jena, Jena, Germany, 1991, pp. 627–634.